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APPLICATION NUMBER: ***60/526,262***
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N. WOODSON
Certifying Officer

MS PROVISIONAL PATENT APPLICATION
PTO/SB/16(8-00)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53 (c).

Filing Date	December 3, 2003	Docket No.	3893-0224P

INVENTOR(s)/APPLICANT(s)

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Bjarne	NØRREMARK	Søborg, Denmark

☐ Additional inventors are being named on the separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

NOVEL HYDROXAMIC ACID ESTERS AND PHARMACEUTICAL USE THEREOF

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☒ Drawing(s) *Number of Sheets:* 1
☐ Application Data Sheet. See 37 CFR 1.76.
☐ Other (specify):

METHOD OF PAYMENT *(check one)*

☐ Applicant claims small entity status. See 37 CFR 1.27.
☒ A check or money order is enclosed to cover the Provisional filing fees.
☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number 02-2448, if necessary.

PROVISIONAL FILING FEE

☐ Small Entity ($80.00)
☒ Large Entity ($160.00)

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

Date: December 3, 2003

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NOVEL HYDROXAMIC ACID ESTERS AND PHARMACEUTICAL USE THEREOF

FIELD OF THE INVENTION

This invention relates to novel hydroxamic acid ester derivatives, processes for the preparation thereof, to said compounds for use in therapy, to pharmaceutical compositions comprising said compounds, to methods of treating diseases comprising administering to a patient in need thereof an effective amount of said compound, and to the use of said compounds in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

This invention relates to novel compounds which can inhibit angiogenesis, i.e. which can inhibit the generation or maturation of new blood vessels. It is believed that said compounds may be beneficial in the treatment of a variety of diseases, such as neoplastic diseases and in particular cancer.

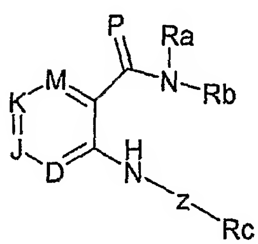
It is now widely accepted that blocking angiogenesis around tumours could be a viable way of treating cancer, possibly as an adjuvant treatment. This is also reflected in the large number of development projects and clinical trials with angiogenesis inhibitors with different inhibitory approaches. It is estimated that more than 300 drug candidates are currently in various stages of testing [Matter, *DDT*, 6, 1005-1024, 2001]. The formation of new blood vessels is a very complex process, which may be targeted in a number of different ways. The candidate drugs, hence, include metalloprotease inhibitors, inhibitors of vascular endothelial growth factor (VEGF) formation, inhibition of VEGF receptors, integrin antagonist, growth factor antibodies, etc.

Of particular interest for the present invention are VEGF receptor inhibitors, most particular VEGF-2 (KDR) receptor inhibitors. The clinically most advanced VEGF receptor inhibitor is semaxanib from Sugen, which was recently discontinued in Phase III studies. Analogues of semaxanib, however, continue to be in development. Another VEGF receptor inhibitor in clinical trial is PTK-787 from Novartis which has recently entered Phase III studies. Bilodeau has reviewed such inhibitors in clinical trials in *Expert Opin. Investig. Drugs.,* 11, 737-745, 2002.

WO 01/29009 and WO 01/58899 describe pyridine derivatives as inhibitors of the VEGF receptor tyrosine kinase and the VEGF-dependent cell proliferation.

WO 02/090346 describes phthalazine derivatives as inhibitors of the VEGF receptor tyrosine kinase with angiogenesis inhibiting activity.

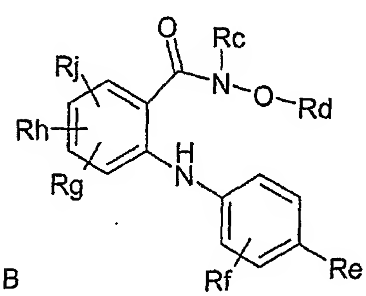
PCT publications WO 00/27819, WO 00/27820, WO 01/55114, WO 01/81311, WO 01/85671, WO 01/85691, WO 01/85715, WO 02/055501, WO 02/066470, WO 02/090349, WO 02/090352, WO 03/000678, WO 02/068406, WO 03/040101, and WO 03/040102 all teach anthranilic acid amide derivatives which include compounds of general structure A, their preparation and their use as VEGF receptor tyrosine kinase inhibitors for the treatment of diseases associated with VEGF-dependent cell proliferation.



A

The use of anthranilic acid amide derivatives for other therapeutic purposes have previously been disclosed in, e.g. US 3,409,688 (analgesic, anti-inflammatory, anti-ulcer), and in EP 564,356 (angiotensin II antagonist).

PCT publications WO 02/06213 and WO 99/01426 teach substituted phenylamino benzhydroxamic acid derivatives which include compounds of general structure B as MEK inhibitors, pharmaceutical compositions and methods of use thereof.



B

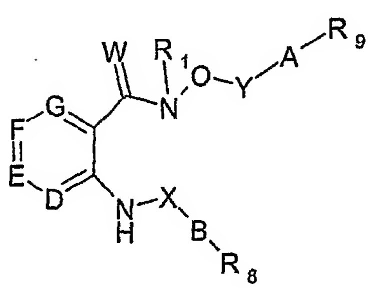
US 5,155,110 teaches hydroxamic acid derivatives having cyclooxygenase and 5-lipoxygenase inhibiting properties and pharmaceutical compositions for treating conditions advantageously affected by the inhibition. The reference fails to describe tyrosine kinase inhibitory activity of the hydroxamic acid ester derivatives disclosed.

SUMMARY OF THE INVENTION

The present inventors have surprisingly found that a novel class of hydroxamic acid esters exhibit a high receptor tyrosine kinase inhibitory activity on a particular VEGF receptor, namely VEGF-R2, frequently referred to as the KDR receptor. The novel hydroxamic acid esters of the present invention may have a number of advantages in comparison to known structurally related anthranilic acid amides.

Compounds of the present invention have improved pharmacokinetic and pharmacodynamic properties such as improved solubility, absorption and metabolic stability in comparison to known structurally related anthranilic acid amides.

Accordingly, the invention relates to compounds of general formula I



[I]

wherein R_1 represents hydrogen or a straight, branched and/or cyclic, saturated or unsaturated hydrocarbon radical, optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, amino, nitro, and cyano;

D represents nitrogen or $C\text{-}R_2$;

E represents nitrogen or C-R_3;

F represents nitrogen or C-R_4;

G represents nitrogen or C-R_5;

R_2, R_3, R_4, and R_5 are the same or different and individually represent hydrogen, halogen, hydroxyl, amino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, or a straight or branched, saturated or unsaturated hydrocarbon radical, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, amino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, and alkylcarbonylamino,
or R_2 and R_3, or R_3 and R_4, or R_4 and R_5 together with the C atoms to which they are attached form a 5- or 6-membered carbocyclic or heterocyclic ring;

W represents oxygen, sulphur, two hydrogen atoms, $=CH_2$, $=N\text{-}O\text{-}R_6$ or the group $=N(R_6)$;

R6 represents hydrogen, hydroxy, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, heteroaryl, alkenyl, alkynyl, or alkyl;

X and Y independently represents a radical of the formula $-(CH_2)_n-$, $-(CH_2)_p\text{-}CH{=}CH\text{-}(CH_2)_q-$, $-(CH_2)_r\text{-}O\text{-}(CH_2)_s$, $-(CH_2)_t\text{-}NH\text{-}(CH_2)_u$, $-(CH_2)_w\text{-}C(O)\text{-}NH\text{-}(CH_2)_z$ where n, p, q, r, s, t, u, w, and z are integers from 0-6, said radical may optionally be substituted by one or more substituents independently selected from the group consisting of R_7;

R_7 represents hydrogen, oxo, halogen, hydroxyl, amino, imino, nitro, carboxy, cyano, cycloalkyl, alkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkenyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, and alkylcarbonylamino, wherein said amino, imino, cycloalkyl, alkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkenyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, aminocarbonyl, and alkylcarbonylamino is optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, oxo,

halogen, hydroxyl, amino, imino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, heterocycloalkyl, aryl, heteroaryl, and alkylaminocarbonyl;

B represents aryl, heteroaryl, heterocycloalkyl, cycloalkyl, or cycloalkenyl, all of which are optionally substituted with one or more substituents independently selected from the group consisting of R_8;

R_8 represents hydrogen, oxo, halogen, hydroxyl, amino, imino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, heterocycloalkyl, aryl or heteroaryl, alkylaminocarbonyl, and a straight or branched, saturated or unsaturated hydrocarbon radical, optionally substituted with one or more substituents independently selected from the group consisting of R_7;

A represents a straight, branched and/or cyclic, saturated or unsaturated hydrocarbon, a heterocycloalkyl, or a heteroaryl,
all of which are optionally substituted with one or more substituents independently selected from the group consisting of R_9;

R_9 represents hydrogen, oxo, halogen, hydroxyl, amino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, alkylaminocarbonyl, heterocycloalkyl, heteroaryl and a straight or branched, saturated or unsaturated hydrocarbon radical,
wherein said straight or branched, saturated or unsaturated alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, aminocarbonyl, alkylcarbonylamino, or alkylaminocarbonyl, heterocycloalkyl, heteroaryl and straight or branched, saturated or unsaturated hydrocarbon radical is optionally substituted by one or more substituents independently selected from the group consisting of R_7;

and pharmaceutically acceptable salts, hydrates, or solvates thereof;

provided that the compound is not
2-[(2-chloro-4-iodophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-N-methyl-benzamide,

2-[(2,6-dichloro-3-methylphenyl)amino]-N-methoxy)-N-methyl-benzamide, or
2-[(2,6-dichlorophenyl)amino]-N-hydroxy-N-methyl-benzamide.

In another aspect, the invention relates to pharmaceutical compositions comprising a compound of formula I or a pharmaceutically acceptable salt, hydrate, or solvate thereof together with a pharmaceutically acceptable vehicle or excipient.

In a further aspect, the invention relates to method of preventing, treating or ameliorating diseases or conditions associated with deregulated angionesis, the method comprising administering an effective amount of a compound according to formula I to a patient in need thereof.

In still a further aspect, the invention relates to the use of compounds according to I for the manufacture of a medicament for the prophylaxis, treatment or amelioration of diseases or conditions associated with deregulated angionesis, such as cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: The structure of the GST-KDR-cyt and the GST-PLCγ fusion protein.

A. A fusion protein containing the intracellular domain (amino acids 793 to 1357) of the KDR and N-terminally tagged to GST was constructed for expression in Sf9 insect cells.
B. A fusion protein containing the two SH2 domains and two phosphorylations sites (amino acids 541 to 797) and N-terminally tagged to GST was constructed and expressed in *E. coli*.

TM: transmembrane domain, GST: glutathione-S-transferase; SH2: Src homology 2 domain; SH3: Src homology 3 domain.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "hydrocarbon radical" is intended to indicate a radical containing only hydrogen and carbon atoms, it may contain one or more double and/or triple carbon-carbon bonds, and it may comprise cyclic moieties in combination with branched or linear moieties. Said hydrocarbon comprises 1-20 carbon atoms, and preferably comprises 1-12, e.g. 1-6, e.g. 1-4, e.g. 1-3, e.g. 1-2 carbon atoms. The term includes alkyl, alkenyl, cycloalkyl, cycloalkenyl, alkynyl and aryl, as indicated below.

In the present context, the term "alkyl" is intended to indicate the radical obtained when one hydrogen atom is removed from a hydrocarbon. Said alkyl comprises 1-20, preferably 1-12, such as 1-6, such as 1-4 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl, *tert.*-butyl, pentyl, isopentyl, hexyl and isohexyl.

The term "halogen" is intended to indicate a substituent form the 7th main group of the periodic table, preferably fluoro, chloro and bromo.

The term "amino" is intended to indicate a radical of the formula $-NR''_2$, wherein each R" independently represents hydrogen or alkyl as indicated above.

The term "imino" is intended to indicate a radical of the formula =NR', wherein R' represents hydrogen or alkyl as indicated above.

The term "alkoxy" is intended to indicate a radical of the formula –OR', wherein R' is alkyl as indicated above, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, etc.

The term "alkylthio" is intended to indicate a radical of the formula –S-R', wherein R' is alkyl as indicated above.

The term "alkoxycarbonyl" is intended to indicate a radical of the formula –C(O)-O-R', wherein R' is alkyl as indicated above, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, etc.

The term "alkylcarbonyloxy" is intended to indicate a radical of the formula –O-C(O)-R', wherein R' is alkyl as indicated above.

The term "alkoxycarbonyloxy" is intended to indicate a radical of the formula –O-C(O)-O-R', wherein R' is alkyl as indicated above.

The term "alkylcarbonyl" is intended to indicate a radical of the formula "-C(O)-R', wherein R' is alkyl as indicated above.

The term "alkoxysulfonyloxy" is intended to represent a radical of the formula $-O-S(O)_2-O-R'$, wherein R' is alkyl as indicated above.

The term "aminosulfonyl" is intended to indicate a radical of the formula $-S(O)_2-R''_2$, wherein each R'' is as indicated above.

The term "alkylsulfonylamino" is intended to indicate a radical of the formula $-NR''-S(O)_2-R'$, wherein R' is alkyl as indicated above, and R'' is as indicated above.

The term "aminocarbonyl" is intended to indicate a radical of the formula $-C(O)-NR''_2$, wherein each R'' is as indicated above.

The term "alkylcarbonylamino" is intended to indicate a radical of the formula $-NR''-C(O)-R'$, wherein R' is alkyl as indicated above, and each R'' is as indicated above.

The term "cycloalkyl" is intended to indicate a saturated cycloalkane radical comprising 3-20 carbon atoms, preferably 3-10 carbon atoms, in particular 3-8 carbon atoms, such as 3-6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

The term "cycloalkenyl" is intended to indicate mono-, di- tri- or tetraunsaturated non-aromatic cyclic hydrocarbonsradicals, comprising 3-20 carbon atoms, typically comprising 3-10 carbon atoms, such as 3-6 carbon atoms, e.g. cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl.

The term "alkenyl" is intended to indicate a mono-, di-, tri-, tetra- or pentaunsaturated hydrocarbon radical comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as 2-4 carbon atoms, e.g. ethenyl, propenyl, butenyl, pentenyl or hexenyl.

The term "alkynyl" is intended to indicate an hydrocarbon radical comprising 1-5 triple C-C bonds and 2-20 carbon atoms, the alkane chain typically comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as 2-4 carbon atoms, e.g. ethynyl, propynyl, butynyl, pentynyl or hexynyl.

The term "aryl" is intended to indicate a radical of aromatic carbocyclic rings comprising 6-20 carbon atoms, such as 6-14 carbon atoms, preferably 6-10 carbon atoms, in particular 5- or 6-membered rings, optionally fused carbocyclic rings with at least one aromatic ring, such as phenyl, naphthyl, indenyl and indanyl.

The term "heteroaryl" is intended to include radicals of heterocyclic aromatic rings comprising 1-6 heteroatoms (selected from O, S and N) and 1-20 carbon atoms, such as 1-5 heteroatoms and 1-10 carbon atoms, such as 1-5 heteroatoms and 1-6 carbon atoms, such as 1-5 heteroatoms and 1-3 carbon atoms, in particular 5- or 6-membered rings with 1-4 heteroatoms selected from O, S and N, or optionally fused bicyclic rings with 1-4 heteroatoms, and wherein at least one ring is aromatic, e.g. pyridyl, quinolyl, isoquinolyl, indolyl, tetrazolyl, thiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thienyl, pyrazinyl, isothiazolyl, benzimidazolyl and benzofuranyl.

The term "heterocycloalkyl" is intended to indicate a cycloalkane radical as defined above, comprising 1-6 heteroatoms, preferably 1-3 heteroatoms, selected from O, N, or S.

The term "carbocyclic" includes aryl, cycloalkanyl, and cycloalkenyl as indicated above.

The term "heterocyclic" includes heteroaryl and heterocycloalkyl as indicated above.

The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula I with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroaetic, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonic, salicylic, succinic, malonic, tartaric, benzenesulfonic, ethane-1,2-disulfonic, 2-hydroxy ethanesulfonic acid, toluenesulfonic, sulfamic or fumaric acid. Pharmaceutically acceptable salts of compounds of formula I may also be prepared by reaction with a suitable base such as sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, silver hydroxide, ammonia or the like.

The term "solvate" is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula I, and a solvent, e.g. alcohol, glycerol or water, wherein said species are in a solid form. When water is the solvent, said species is referred to as a hydrate.

Preferred embodiments of compounds of formula I

In a currently preferred embodiment of the invention W represents oxygen.

In another preferred embodiment of the invention R_1 represents hydrogen.

In another preferred embodiment of the invention D is C-R_2, E is C-R_3, F is C-R_4, and G is C-R_5.

In another preferred embodiment of the invention R_2, R_3, R_4, and R_5 are hydrogen.

In another preferred embodiment of the invention D is nitrogen, E is C-R_3, F is C-R_4, and G is C-R_5.

In another preferred embodiment of the invention R_3, R_4, and R_5 are hydrogen.

In another preferred embodiment the ring-structure B represents substituted or unsubstituted pyridyl, such as 2- pyridyl, 3- pyridyl, or 4-pyridyl.

In another preferred embodiment the ring-structure B represents substituted or unsubstituted phenyl.

In another preferred embodiment R_8 is hydrogen, chloro, bromo, fluoro, or methoxy.

In another preferred embodiment X is a bond, $-CH_2-$, or -CH=CH-.

In another preferred embodiment Y is radical of the formula $-(CH_2)_n-$, where n is an integer from 0-6; or Y is radical of the formula $-(CH_2)_p-C(O)-NH-(CH_2)_q$, where p is an integer from 0-6 and q is 0; or Y is radical of the formula $-(CH_2)_r-O-(CH_2)_s$, where r is an integer from 0-6 and s is 0.

In another preferred embodiment Y is a bond, $-CH_2-$, or $-CH(CH_3)-$, $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-$, $-CH_2-C(O)-$, or $-CH_2-C(O)-NH-$.

In another preferred embodiment A represents substituted or unsubstituted (C_6-C_{10})aryl, or substituted or unsubstituted (C_{3-10})heterocycloalkyl, or substituted or unsubstituted (C_2-C_{10})heteroaryl.

In another preferred embodiment A represents substituted or unsubstituted phenyl, substituted or unsubstituted (C_5)heteroaryl, or substituted or unsubstituted (C_9)heteroaryl.

In another preferred embodiment A represents substituted or unsubstituted phenyl, substituted or unsubstituted thiazol, or substituted or unsubstituted quinoline.

In another preferred embodiment R10 is nitro, fluoro, chloro, bromo, methoxy, hydrogen, carbomethoxy, cyano, or methyl.

In another preferred embodiment B-R_8 represents 4-pyridyl, 4-fluorophenyl, or 4-methoxyphenyl.

In another preferred embodiment A-R_9 represents 2-nitrophenyl, 4-nitrophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-methoxyphenyl, 3,4,5-trimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2,3-dichlorophenyl, 3,6-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 6-fluoro-2-chlorophenyl, 4-fluoro-2-chlorophenyl, 2-fluoro-3-chlorophenyl, 4-

carbomethoxyphenyl, 4-cyanophenyl, quinolin-2-yl, phenyl, 2-methylthiazol-4-yl, or 4-methoxyphenyl.

In particular compounds of formula I may be selected amongst the list consisting of
N-Benzyloxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 1),
N-(4-Nitro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 2),
N-(2-Nitro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 3),
2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethyl-benzyloxy)-benzamide (compound 4),
2-[(Pyridin-4-ylmethyl)-amino]-N-(2-trifluoromethyl-benzyloxy)-benzamide (compound 5),
N2-[(Pyridin-4-ylmethyl)-amino]-N-(4-trifluoromethyl-benzyloxy)-benzamide (compound6),
N-(4-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 7),
N-(3-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 8),
2-[(pyridin-4-ylmethyl)-amino]-N-(3,4,5-trimethoxy-benzyloxy)-benzamide (compound 9),
N-(4-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 10),
N-(3-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 11),
N-(2-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 12),
N-(2-Bromo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 13),
N-(2,4-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 14),
N-(3,4-Dichloro-benzyloxy)-2-[(pyridine-4-ylmethyl)-amino]-benzamide (compound 15),
N-(2,6-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 16),
N-(3,5-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 17),
N-(2,3-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 18),
N-(2,5-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 19),
N-(2-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 20),
N-(3-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 21),
N-(4-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 22),
N-(2-Chloro-6-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 23),
N-(2-Chloro-4-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 24),
N-(3-Chloro-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 25),
4-{2-[(pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid methyl ester (compound 26),
N-(4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 27),
2-[(Pyridin-4-ylmethyl)-amino]-N-(quinolin-2-ylmethoxy)-benzamide (compound 28),
N-Phenoxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 29),

N-(2-Phenoxy-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 30),
N-(3-Phenyl-propoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 31),
N-(2-methyl-thiazol-4 ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 32),
N-Benzyloxy-2-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide (compound 33),
2-(4-Fluoro-benzylamino)-N-(4-methoxy-benzyloxy)-nicotinamide (compound 34),
2-(4-methoxy-benzylamino)-N-(4-methoxy-benzyloxy)-nicotinamide (compound 35),
N-(1-Phenyl-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-phenoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(Pyridin-2-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(thiazol-4-ylmethoxy)-benzamide,
N-(2-Chloro-thiazol-5-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Phenyl-thiazol-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2,6-Dichloro-pyridin-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(2,3,5,6-tetrafluoro-4-methoxy-benzyloxy)-benzamide,
N-(4-Methoxy-3-trifluoromethyl-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethoxy-benzyloxy)-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(4-trifluoromethoxy-benzyloxy)-benzamide,
N-(6-Chloro-benzo[1,3]dioxol-5-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Bromo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Iodo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(3-Iodo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
3-{2-[(Pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid methyl ester,
3-{2-[(Pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid,
N-[4-(Morpholine-4-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-{3-[4-(3-Cyano-pyridin-2-yl)-piperazine-1-carbonyl]-benzyloxy}-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[4-(4-Methyl-piperazine-1-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(4-Methyl-piperazine-1-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(Morpholine-4-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(3-Hydroxy-pyrrolidine-1-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(3-Bromo-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,

N-(2-Chloro-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-2-methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-naphthalen-1-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
Acetic acid 2-[3-(2-{2-[(pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-phenyl)-prop-2-ynyloxy]-ethyl ester,
N-[2-(3-Hydroxy-prop-1-ynyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(3-Hydroxy-prop-1-ynyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(5-Cyano-pent-1-ynyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(4-vinyl-benzyloxy)-benzamide,
N-(2-Morpholin-4-yl-2-oxo-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[(2-Methoxy-phenylcarbamoyl)-methoxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-Methoxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(tetrahydro-pyran-2-yloxy)-benzamide,
N-Benzyloxy-2-[(thiazol-5-ylmethyl)-amino]-benzamide,
N-(2,4-Dichloro-benzyloxy)-2-[(thiazol-5-ylmethyl)-amino]-benzamide,
N-Benzyloxy-2-[(6-chloro-imidazo[2,1-b]thiazol-5-ylmethyl)-amino]-benzamide,
N-Benzyloxy-2-[(2-methyl-imidazo[1,2-a]pyrimidin-3-ylmethyl)-amino]-benzamide,
N-(2,4-Dichloro-benzyloxy)-2-[(2,6-dimethoxy-pyrimidin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(2-Chloro-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(4-Cyano-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(3-Bromo-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(2-Iodo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(4-Cyano-2-methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(2-Methyl-thiazol-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-Benzyloxy-2-(isoquinolin-5-ylamino)-nicotinamide,
N-Benzyloxy-2-(4-methoxy-benzylamino)-nicotinamide,
N-Benzyloxy-2-(4-fluoro-benzylamino)-nicotinamide,
N-Benzyloxy-2-(4-chloro-benzylamino)-nicotinamide,
N-(4-Methoxy-benzyloxy)-2-[2-(4-methoxy-phenyl)-vinyl]-nicotinamide,
N-(4-Chloro-benzyloxy)-2-(4-cyano-benzylamino)-benzamide,
2-[4-(Methoxyimino-methyl)-benzylamino]-N-(2-methyl-thiazol-4-ylmethoxy)-benzamide,
N-(4-Cyano-2-methoxy-benzyloxy)-3-[(pyridin-4-ylmethyl)-amino]-isonicotinamide,
N-Benzyloxy-3-[(pyridin-4-ylmethyl)-amino]-isonicotinamide,
N-(2-Methyl-thiazol-4-ylmethoxy)-3-[(pyridin-4-ylmethyl)-amino]-isonicotinamide,
5-Methyl-N-(2-methyl-thiazol-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
and N-Hydroxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide.

The compounds of formula I may be obtained in crystalline form either directly by concentration from an organic solvent or by crystallisation or recrystallisation from an organic solvent or mixture of said solvent and a cosolvent that may be organic or inorganic, such as water. The crystals may be isolated in essentially solvent-free form or as a solvate, such as a hydrate. The invention covers all crystalline modifications and forms and also mixtures thereof.

Compounds of formula I may comprise asymmetrically substituted (chiral) carbon atoms and carbon-carbon double bonds which may give rise to the existence of isomeric forms, e.g. enantiomers, diastereomers and geometric isomers. The present invention relates to all such isomers, either in pure form or as mixtures thereof. The invention also relates to all possible tautomers of the compounds of formula I.

Formation of new blood vessels takes place in a balance between compounds working for and against this formation, i.e. in a balance between pro-angiogenic and anti-angiogenic compounds. Early in development, proliferating and differentiating endothelial cells form vessels in previously avascular tissue. This first stage is a leaky network which has to be remodelled to reach a mature vessel. This process is referred to as vasculogenesis. Formation of a new blood vessel may also occur from an already existing blood vessel in a process referred to as angiogenic sprouting. Here, the "old" vessel is initially destabilised at a located site, and the new vessel is formed from there and is subsequently matured.

The processes above commonly involve the vascular endothelial, which is a particular type of endothelium composed by a single layer of smooth cells that cover the lumen of blood vessels. A number of specific growth factors acting on said endothelial have been identified, and they include five members of the vascular endothelial growth factor (VEGF) family, four members of the angiopoietin family, and one member of the large ephrin family. VEGF, however, holds the position as the most critical driver of vascular formation as it is required to initiate the formation of immature vessels both by vasculogenesis and angiogenic sprouting [Yancopoulos, *Nature*, 407, 242-248, 2000]. VEGF, originally termed "Vascular Permeability Factor" (VPF) is the angiogenic factor which lies at the centre of the network regulating the growth and differentiation of the vascular system and its components during embryonic development, normal growth and in a wide number of pathological anomalies along with its cellular receptors [G. Breier et al., Trends in Cell Biology 6, 454-6, 1996].

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein related to "Platelet-Derived Growth Factor" (PDGF); it is produced by normal cell lines and tumour cell lines; it is an endothelial cell-specific mitogen; shows angiogenic activity in *in vivo* test systems (e.g. rabbit cornea); is chemotactic for endothelial cells and monocytes; and induces plasminogen activators in endothelial cells, which are involved in the proteolytic degradation of extracellularmatrix during the formation of capillaries. A number of isoforms of VEGF are known, which show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as "Placenta Growth Factor" (PlGF) and VEGF-C.

VEGF's are unique in that they are the only angiogenic growth factors known to contribute to vascular hyperpermeability and the formation of edema. Indeed, vascular hyperpermeability and edema that is associated with the expression or administration of many other growth factors appears to be mediated via VEGF production. Inflammatory cytokines stimulate VEGF production. Hypoxia results in a marked upregulation of VEGF in numerous tissues, hence situations involving infarct, occlusion, ischemia, anemia, or circulatory impairment typically invoke VEGF/VPF-mediated responses, Vascular hyperpermeability, associated edema, altered transendothelial exchange and macromolecular extravasation, which is often accompanied by diapedesis, can result in excessive matrix deposition, aberrant stromal proliferation, fibrosis, etc. Hence, VEGF-mediated hyperpermeability can significantly contribute to disorders with these etiologic features. As such, regulators of angiogenesis have become an important therapeutic agent.

Three VEGF receptors are known, VEGFR-1 (or fms-like tyrosine kinase receptor (Flt-1)), VEGFR-2 and VEGFR-3, and they are expressed almost exclusive on endothelial cells. VEGFR-2 was previously referred to as KDR (kinase insert domain-containing receptor), and this receptor appears to play a crucial role in the induction of cell proliferation by VEGF [Ellis, *Seminars in Oncology*, 28, 94-104, 2001]. The VEGF receptors belong to the group of tyrosine kinease receptors, and they are composed of seven extracellular Ig-like domains, harbouring the VEGF binding site, and an intracellular tyrosine kinase domain. The intra- and extracellular domains are connected by a short transmembrane segment [Shawver, *DDT*, 2, 50-63, 1997]. Like other receptor tyrosine kinases, VEGFR-2 dimerise upon binding to VEGF, and the tyrosine kinase domain becomes autophophorylated. This activated form, in turn, binds to other molecules which are activated, e.g. by yet another phosphorylation. This cascade eventually triggers the proliferation of endothelial cells, and thus the formation of new blood vessels.

Tumour cells require oxygen to grow and to metastasize. Oxygen has a very limited diffusion range, so for the tumour to grow beyond a very limited size, they cannot rely on passive oxygen transport, but rather they have to establish an active oxygen transport, i.e. they have to attract blood vessels from the host. Nutrients, required by the tumour, are also supplied through the blood vessels. A tumour will start in or eventually expand into an avascular area resulting in low pO_2 and pH, and these factors trigger an upregulation of, e.g. VEGF in the tumour cells. Without sufficient oxygen and nutrient supply, the tumour cells become necrotic or apoptotic, and the tumour cell will thus cease to grow, and may even regress. Angiogenesis is regarded as an absolute prerequisite for tumours which grow beyond a diameter of about 1-2-mm; up to this limit, oxygen and nutrients may be supplied to the tumour cells by diffusion. Every tumour, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size. A large number of human tumours, especially gliomas and carcinomas, express high levels of VEGF and its receptors. This has led to the hypothesis that the VEGF released by tumor cells stimulates the growth of blood capillaries and the proliferation of tumour endothelium in a paracrine manner and through improved blood supply, accelerate tumour growth. Increased VEGF expression could explain the occurrence of cerebral edema in patients with glioma. Direct evidence of the role of VEGF as a tumour angionesis factor in vivo is shown in studies in which VEGF expression or VEGF activity was inhibited. This was achieved with anti-VEGF antibodies, with dominant-negative VEGFR-2 mutants which inhibited signal transduction, and with antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumour cell lines in vivo as a result of inhibited tumour angiogenesis. Already in 1971 Folkman suggested that inhibition of angiogenesis could be a strategy for treating cancers which are manifested by solid tumours [Folkman, in Cancer Medicine, (Eds Holland et al), 132-152, Decker Ontario, Canada, 2000]. This notion was based on even earlier observations that angiogenesis occurs around tumours, and on hypotheses that an "angiogenic" principle was produced by the tumours.

Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumours: 1) inhibition of the growth of vessels, especially capillaries, into vascular resting tumours, with the result that there is no net tumour growth owing to the balance that is achieved between apoptosis and proliferation; 2) prevention of the migration of tumour cells owing to the absence of blood flow to and from tumours; and 3) inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels [R. Connell et al., Exp. Opin. Ther. Patents, 11, 77-114, 2001]. As mentioned above, the compounds of the present invention inhibit VEGFR-2 (KDR), and therefore prevent

angiogenesis, i.e. the formation of new blood vessels, and they will thus cause the tumour to cease growing and perhaps even to regress.

Compounds of the invention would be useful for the prophylaxis, treatment or amelioration of a disease or condition associated with deregulated angionesis, such as the prophylaxis, treatment or amelioration of tumours or neoplastic diseases including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, urinary tract, breast, intestine, colon, kidney, liver, small or non-small cell lung carcinoma, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, head, brain, neck, uterus, and skin (including squamous cell carcinoma); hematopoietic tumours of lymphoid lineage (including leukaemia, acute lymphocitic leukaemia, acute lymphoblastic leukaemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's disease lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumours of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukaemia); tumours of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumours of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumours (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

Preferably, the compounds may be useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

The blood vessels are also of major importance when the tumours metastasize, as the metastases are transported in the blood stream. A reduced number of blood vessels in and around the tumour reduces the metastatic potential of a tumour. The invention thus also provides a method of reducing the metastatic potential of a tumour.

Very small tumours may survive even in lack of adequate vasculature, and such tumours may start to grow and induce angiogenesis if the anti-angiogenic treatment is stopped. It therefore believed that treatment with compounds of the present invention may beneficially include co-administration or combination therapy of other therapeutically active compounds typically used in the treatment of tumours or cancer, such as chemotherapeutic agents, cytotoxic agents, and anticancer agents. The other therapeutically active compounds also include other inhibitors of protein kinases, such as tyrosine kinases useful in the treatment of tumours or cancer. The other therapeutically active compounds may be administered

concomitantly or sequentially, and it lies within the capabilities of a skilled physician or veterinary to decide a dosing regime which fits best to the needs of the patient. The therapeutic agents may also be given as a single composition, such as in a single capsule or tablet having a fixed ratio of the active agents. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known chemotherapeutic, cytotoxic, or anticancer agent.
Therapeutically active compounds typically used in the treatment of tumours or cancer include S-triazine derivatives such as altretamine; enzymes such as asparaginase; antibiotic agents such as bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin, epirubicin and plicamycin; alkylating agents such as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine and thiotepa; antimetabolites such as cladribine, cytarabine, floxuridine, fludarabine, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, gemcitabin, pentostatin and thioguanine; antimitotic agents such as etoposide, paclitaxel, teniposide, vinblastine, vinorelbin and vincristine; hormonal agents, e.g. aromatase inhibitors such as aminoglutethimide, corticosteroids, such as dexamethasone and prednisone, and luteinizing hormone releasing hormone (LH-RH); antiestrogens such as tamoxifen, formestan and letrozol; antiandrogens such as flutamide; biological response modifiers, e.g. lymphokines such as aldesleukin and other interleukines; interferon such as interferon-α; growth factors such as erythropoietin, filgrastim and sagramostim; differentiating agents such as vitamin D derivatives and all-trans retinoic acid; immunoregulators such as levamisole; and monoclonal antibodies, tumour necrosis factor α and angiogenesis inhibitors. Finally, ionising radiation (radiation therapy) , although not readily defined as a compound, is heavily depended on in the treatment of tumours, and may be combined with the compounds of the present invention in. Due to the severe side effects often experienced by patients receiving anti-tumour treatment it is often desirable also to administer therapeutica which are do themselves treat the tumour, but rather help relieving the side effects. Such compounds include amifostin, leucovorin and mesna.

Pathological or deregulated angiogenesis is not only connected to tumours, but has also been implicated in a number of other pathological conditions or diseases (see P. Carmeliet & R.K. Jain, Nature, Vol. 407, 2000, pp. 249-257; A.H. Vagnucci & W.W. Li, The Lancet, Vol. 361, 2003, 605-608; B. Xuan et al., J. Ocular Pharmacology & Therapeutics, Vol. 15(2), 1999, pp. 143-152) associated with deregulated angiogenesis. Compounds of the present invention would be useful for, but are not limited to the prevention, prophylaxis, treatment

or amelioration of a disease or condition associated or related with deregulated angionesis. These conditions or diseases include conditions or diseases charaterised by abnormal angiogenesis or vascular malfunction, atherosclerosis, haemangioma, haemangioendothelioma, warts, pyogenic granulomas, hair growth, scar keloids, allergic oedema, dysfunctional uterine bleeding, follicular cysts, ovarian hyperstimulation, endometriosis, obesity, arthritis, rheumatoid arthritis, synovitis, bone and cartilage destruction, osteomyelitis, pannus growth, osteophyte formation, inflammatory and infectious diseases (hepatitis, pneumonia, glomerulonephritis), asthma, nasal polyps, transplantation, liver regeneration, retinopathy, diabetic retinopathy, endometriosis, psoriasis, lymphoproliferative disorders, thyroiditis, thyroid enlargement, obstructive lung disease, or cerebral ischaemia reperfusion injury, Alzheimer's disease, and eye diseases such as such as acute macular degeneration, age-related macular degeneration and ischemic retinopathy.

Besides being useful for human treatment, the compounds of the present invention may also be useful for veterinary treatment of animals including mammals such as horses, cattle, sheep, pigs, dogs, and cats.

For use in therapy, compounds of the present invention are typically in the form of a pharmaceutical composition or pharmaceutical formulation. The invention therefore relates to a pharmaceutical composition comprising a compound of formula I, optionally together with one or more other therapeutically active compounds, such as chemotherapeutic agents, anticancer agents, cytotoxic agents, together with a pharmaceutically acceptable excipient or vehicle. Examples of such other therapeutically active compounds include those typically used in the treatment of tumours or cancer listed above. The excipient must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof.

If the treatment involves administration of another therapeutically active compound it is recommended to consult *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9^{th} Ed., J.G. Hardman and L.E. Limbird (Eds.), McGraw-Hill 1995, for useful dosages of said compounds.

Conveniently, the active ingredient comprises from 0.1-99.9% by weight of the composition.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers. In the form of a dosage unit, the compound may be administered one or more times a day at appropriate intervals, always depending, however, on the condition of the patient, and in accordance with the prescription made by the medical practitioner. It is also envisaged that in certain treatment regimes, administration with longer intervals e.g. every other day, every week, or even with longer intervals may be beneficial.

Conveniently, dosage unit of a formulation contains between 0.01 mg and 10000 mg, preferably between 100 mg and 3000 mg, such as between 200 mg and 1000 mg of a compound of formula I.

The formulations include e.g. those in a form suitable for oral (including sustained or timed release), rectal, parenteral (including subcutaneous, intraperitoneal, intramuscular, intraarticular and intravenous), transdermal, ophthalmic, topical, nasal or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy, e.g. as disclosed in Remington, The Science and Practice of Pharmacy, 20th ed., 2000. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid, such as ethanol or glycerol; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Such oils may be edible oils, such as e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carbomers

and polyvinylpyrrolidone. The active ingredients may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form such as a powder or granules, optionally mixed by a binder, such as e.g. lactose, glucose, starch, gelatine, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyethylene glycol, waxes or the like; a lubricant such as e.g. sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as e.g. starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the like or a dispersing agent, such as polysorbate 80. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of suppositories in which the compound of the present invention is admixed with low melting water soluble or insoluble solids such as cocoa butter, hydrogenated vegetable oils, polyethylene glycol or fatty acids esters of polyethylene glycols, while elixirs may be prepared using myristyl palmitate.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. The formulation may be conveniently sterilised by for instance filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in *e.g.* Encyclopedia of Pharmaceutical Technology, vol.9, 1994, are also suitable for parenteral administration.

Alternatively, the compound of formula I may be presented as a sterile, solid preparation, *e.g.* a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

Transdermal formulations may be in the form of a plaster or a patch.

Formulations suitable for ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients, which may be in microcrystalline form, for example, in

the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems e.g. as disclosed in Encyclopedia of Pharmaceutical Tehcnology, vol.2, 1989, may also be used to present the active ingredient for ophthalmic administration.

Formulations suitable for topical or ophthalmic administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers. Such formulations are disclosed in greater detail in e.g. Modern Pharmaceutics, 2nd ed., G.S. Banker and C.T. Rhodes (Eds.), page 427-432, Marcel Dekker, New York; Modern Pharmaceutics, 3th ed., G.S. Banker and C.T. Rhodes (Eds.), page 618-619 and 718-721, Marcel Dekker, New York and Encyclopedia of Pharmaceutical Technology vol. 10, J Swarbrick and J.C. Boylan (Eds), page 191-221, Marcel Dekker, New York

In addition to the aforementioned ingredients, the formulations of a compound of formula I may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourant, surface active agents, thickeners, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

When the active ingredient is administered in the form of salts with pharmaceutically acceptable non-toxic acids or bases, preferred salts are for instance easily water-soluble or slightly soluble in water, in order to obtain a particular and appropriate rate of absorption.

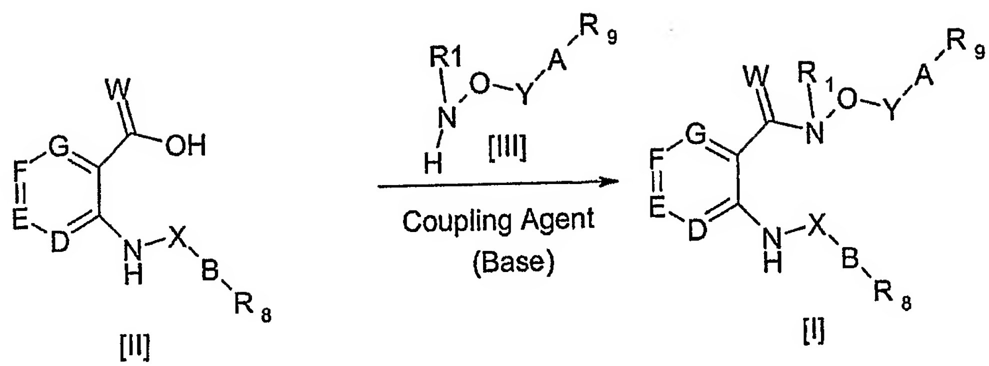
METHODS OF PREPARATION

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. The compounds of the present invention can be synthesised using the methods outlined below, together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below.
The novel compounds of formula (I) may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction

conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognised by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the starting molecule in a reaction must be compatible with the reagents and reactions proposed. Not all compounds of formula (I) falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods can be used.

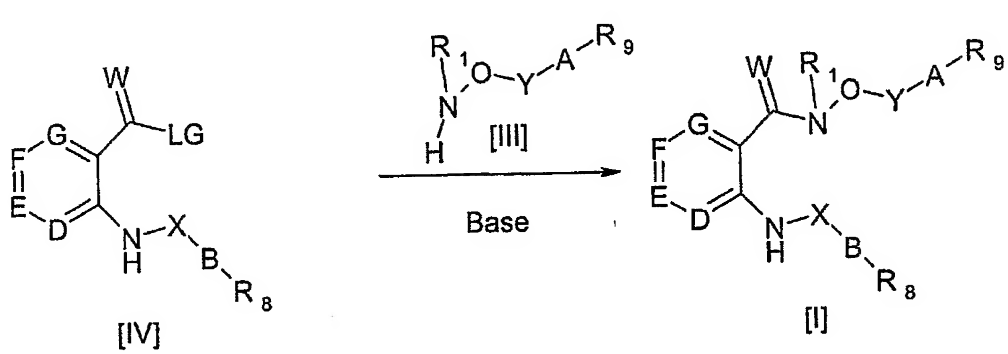
The compounds of formula (I) can be prepared by techniques and procedures readily available to one of ordinary skill in the art, for example by following the procedures as set forth in the following Schemes. These Schemes are not intended to limit the scope of the invention in any way. All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

The compounds of formula (I) are generally obtained by condensation of acids of general formula (II) and O-substituted (Y-A-R_9) hydroxylamines of general formula (III) by action of coupling agent, such as a peptide coupling agent, optionally in the presence of a base, in an appropriate solvent as shown in Scheme 1. Preferred coupling agents include N,N'-carbonyldiimidazole (CDI), diphenylphoshinic chloride (DPP-Cl), benzotriazol-yloxy-tripyrolidinophosphonium hexafluorophosphate (PyBOP), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), N,N'-dicyclohexylcarbodiimide (DCC), or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI). Preferred bases include diisopropylethylamine, triethylamine, 4-methylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or pyridine or a substituted pyridine, for example 4-dimethylaminopyridine or 2,6-dimethylpyridine. Preferred solvents are polar aprotic solvents such as dichloromethane, tetrahydrofuran, 1-methyl-2-pyrrolidinone, or dimethylforamide. The reactions are generally carried out at a temperature between about −78°C to about 60°C, and are normally complete within about 2 hours to about 5 days. The product hydroxamic acid esters of general structure (I) can be isolated by extraction with a suitable organic solvent, preferably a non-water miscible solvent such as ethyl acetate after dilution of the reaction mixture with water. Evaporation of the solvent under reduced pressure affords the products that may be further purified, if desired, by standard methods such as chromatography, crystallisation, or distillation. Alternatively, the products can be isolated by removing the solvent used to perform the reaction in, for example by evaporation under reduced pressure and further purified as mentioned above.



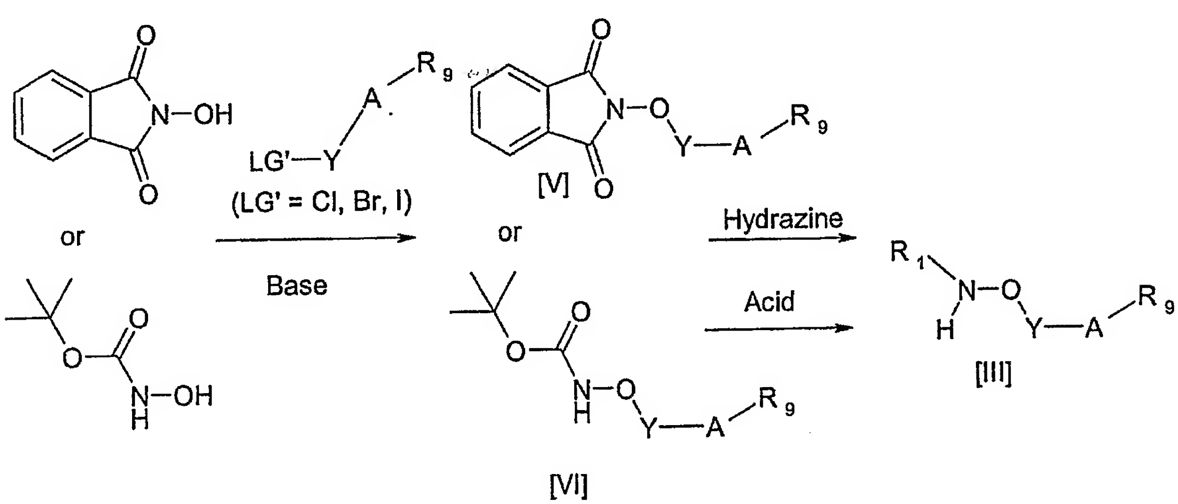
Scheme 1: General method for the preparation of benzamides of general formula (I) from acids of general formula (II)

The disclosed compounds may also generally be prepared as shown in Scheme 2 by the reaction of O-substituted (Y-A-R_9) hydroxylamines of general formula (III) with "activated" acids of general formula IV, wherein "LG" is a leaving group. Compounds of general structure IV include, but are not limited to, acid halides, anhydrides, mixed anhydrides, or an activated esters, e.g. pentafluorophenyl esters, nitrophenyl esters or thioesters. The reaction is preferably carried out in the presence of base such as diisopropylethylamine, triethylamine, 4-methylmorpholine, or pyridine or a substituted pyridine, for example 4-dimethylaminopyridine or 2,6-dimethylpyridine. Preferred solvents include polar aprotic solvents such as dichloromethane, tetrahydrofuran, 1-methyl-2-pyrrolidinone, or dimethylformamide. The synthesis of obtain hydroxamic acid esters from pentafluorophenyl esters of benzoic acid derivatives has been previously described in WO 02/06213.



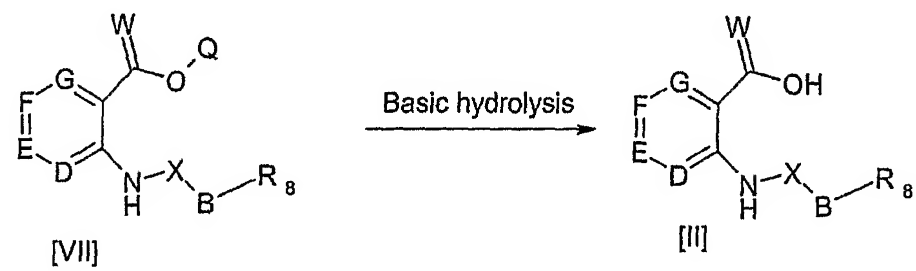
Scheme 2: General method for the preparation of benzamides of general formula (I) from "activated" acids of general formula (IV)

The starting materials O-substituted (Y-A-R_9) hydroxylamines of general formula (III) are either commercially available or can be readily prepared using procedures well-known to a person skilled in the art. Non-limiting examples of such preparations have been described by e.g. J.N. Kim *et al.*: *Synthetic Communications*, (1992) 22, 1427-1432, M. Arimoto *et al.*: *The Journal of Antibiotics* (1988) XLI, 12, 1795-1811, H.M. Petrassi *et al.*: *Organic Lettres* (2001), 3, 139-142, E. Grochowski, J. Jurczak: *Synthesis* (1976), 682-684, and WO 02/06213. Typical but non-limiting synthetic routes to obtain O-substituted Y-A-R_9) hydroxylamines of general formula (III) is illustrated in Scheme 3: Reaction of N-hydroxyphthalimide or *tert*-butyl-N-hydroxycarbamate with an alkylating agent, e.g. an alkyl halide (LG-Y-A-R_9), in a suitable solvent in the presence of a base such as triethylamine, 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU), potassium carbonate, or caesium carbonate, afford intermediates of general formula V or VI respectively. Reaction of V with hydrazine affords the desired O-substituted (Y-A-R_9) hydroxylamines of general formula (III). Treatment of VI with acid, e.g. trifluoroacetic acid or hydrochloric acid also yields the desired O-substituted (Y-A-R_9) hydroxylamines of general formula (III). The O-substituted (Y-A-R_9) hydroxylamines of general formula (III) may be isolated and used either as free amines or as the corresponding salts, e.g. hydrochloric acid salts.



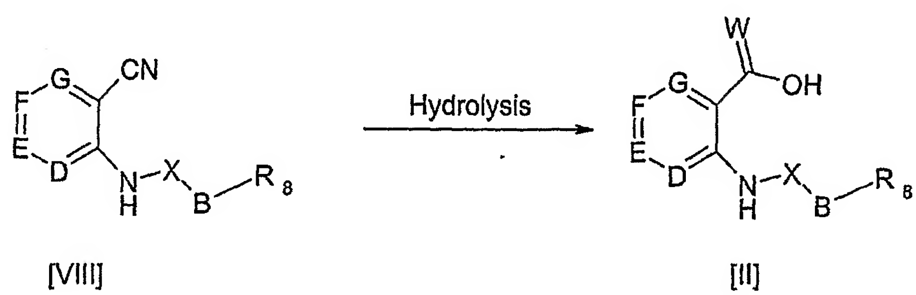
Scheme 3: Methods for preparation of O-substituted (Y-A) hydroxylamines of general formula (III) (R1 = H).

The acids of formula (II) (in which W is oxygen) may be prepared from esters of general formula (VII) (in which Q e.g. represents alkyl or substituted alkyl) by hydrolysis, such as base catalysed hydrolysis, acid catalysed, or enzyme mediated hydrolysis, as shown in Scheme 4. Non-limiting examples of bases which can be used are lithium hydroxide, sodium hydroxide or potassium hydroxide.



Scheme 4: General method for the preparation of acids of general formula II from esters of general formula (VII)

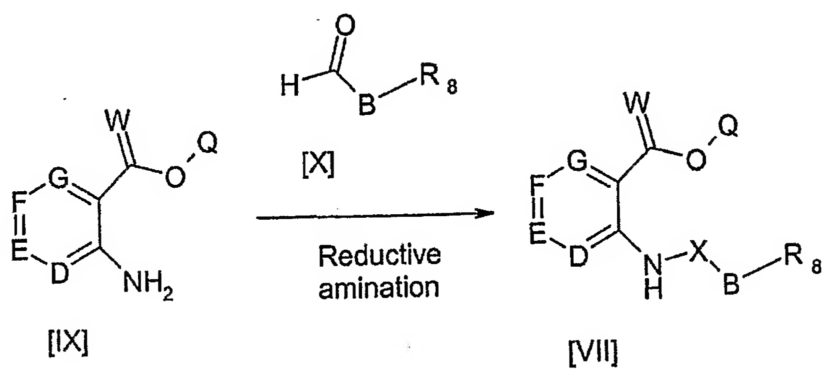
Alternatively, the acids of general formula (II) (in which W is oxygen) may be prepared by hydrolysis of nitriles of general formula (VIII) as shown in Scheme 5, such as by basic, acidic, or enzymatic hydrolysis.



Scheme 5: General method for the preparation of acids of general formula II from nitriles of general formula (VIII)

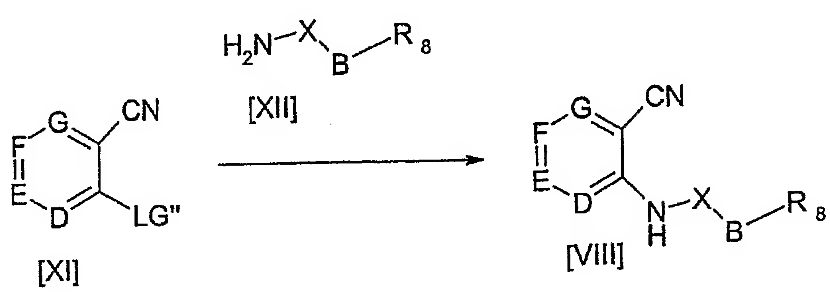
Esters of general formula (VII) may be prepared from the corresponding amines of general formula (IX) and aldehydes of general formula (X) (obtainable from commercial sources or prepared as e.g. described in WO 02/090352) e.g. by reductive amination, (see for example: A.F. Abdel-Magid *et al.*: *J. Org. Chem.* (1996), 61, 3849-3862, WO 00/27819,

and WO 02/090352) as shown in Scheme 6. Suitable reducing agents are e.g. sodium cyanoborohydride, sodium borohydride, or sodium triacetoxyborohydride. Amines of general formula IX are either readily prepared by a person skilled in the art or are commercially available.



Scheme 6: General method for the preparation of esters of general formula (VII) from amines of general formula (IX)

Nitriles of formula (VIII) (e.g. in which D represents nitrogen) can for example be prepared by reaction of compounds of general formula (XI) (in which LG" represents a suitable leaving group such as halogen, e.g. fluorine or chlorine) with amines of general formula (XII) (for examples see R. Kwok. *J. Heterocyclic Chem.* (1978) 15, 877-880; S. Brunel *et al. J. Heterocyclic Chem.* (1980) 17, 235-240) as shown in Scheme 7. Compounds of general formula XI are either readily prepared by a person skilled in the art or are commercially available.



Scheme 7: General preparation of nitriles of general formula (VIII) from nitriles of general formula (XII)

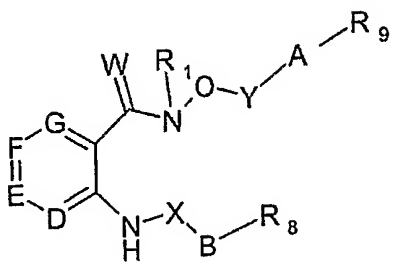
GENERAL PROCEDURES, PREPARATIONS AND EXAMPLES

The exemplified compounds of general formula (I) are listed in Table 1. For ^1H nuclear magnetic resonance (NMR) spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values (δ) (in ppm) are quoted for dimethyl-d_6 sulfoxide (DMSO-d_6) solutions relative to internal tetramethylsilan (δ = 0) standard. The value of a multiplet, either defined (doublet (d), triplet (t), quartet (q)) or not (m) at the approximate mid point is given unless a range is quoted, (bs) indicates a broad singlet. The organic solvents used were anhydrous unless otherwise specified. The reactions were preferably carried out under an inert atmosphere such as under nitrogen or argon. Chromatography was performed on silica gel (from Merck, 0.040-0.063 mm). Selected compounds or intermediates were commercially available from e.g. Aldrich, SPECS, or Bionet research intermediates.

The following abbreviations have been used throughout:

Brine	saturated aqueous sodium chloride
Boc	tert-Butoxycarbonyl
DMF	*N,N'*-Dimethylformamide
EtOAc	Ethyl acetate
e.q.	equivalent
M	Molar (mol/L)
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
THF	Tetrahydrofuran

Table 1:
Compounds of general formula (I)



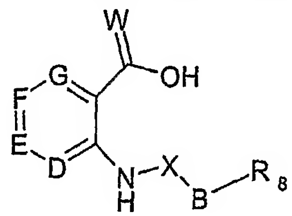
[I]

Compound	Example	D	E	F	G	W	R_1	X	$B-R_8$	Y	$A-R_9$
1	1	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	phenyl
2	2	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-nitrophenyl
3	3	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2-nitrophenyl
4	4	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3-trifluoro-methylphenyl
5	5	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2-trifluoro-methylphenyl
6	6	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-trifluoro-methylphenyl
7	7	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-methoxy-phenyl
8	8	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3-methoxy-phenyl
9	9	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3,4,5-tri-methoxyphenyl
10	10	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-chlorophenyl
11	11	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3-chlorophenyl
12	12	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2-chlorophenyl
13	13	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2-bromophenyl
14	14	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2,4-dichloro-phenyl
15	15	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3,4-dichloro-phenyl

16	16	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2,6-dichloro-phenyl
17	17	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3,5-dichloro-phenyl
18	18	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2,3-dichloro-phenyl
19	19	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3,6-dichloro-phenyl
20	20	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2-fluorophenyl
21	21	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	3-fluorophenyl
22	22	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-fluorophenyl
23	23	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	6-fluoro-2-chlorophenyl
24	24	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-fluoro-2-chlorophenyl
25	25	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	2-fluoro-3-chlorophenyl
26	26	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-carbomethoxy-phenyl
27	27	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	4-cyanophenyl
28	28	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	quinolin-2-yl
29	29	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	bond	phenyl
30	30	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-(CH_2)_2-O-$	phenyl
31	31	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-(CH_2)_3-$	phenyl
32	32	CH	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-(CH_2)_3-$	2-methylthiazol-4-yl
33	33	N	CH	CH	CH	O	H	$-CH_2-$	4-pyridyl	$-CH_2-$	phenyl
34	34	N	CH	CH	CH	O	H	$-CH_2-$	4-fluoro-phenyl	$-CH_2-$	4-methoxy-phenyl
35	35	N	CH	CH	CH	O	H	$-CH_2-$	4-methoxy-phenyl	$-CH_2-$	4-methoxy-phenyl

Table 2:

Exemplified intermediates of general formula II

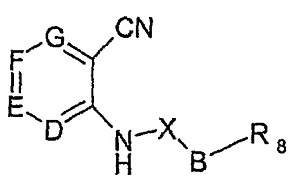


[II]

Preparation	D	E	F	G	W	X	B-R_8
1	C	C	C	C	O	$-CH_2-$	pyridin-4-ylmethyl
2	N	C	C	C	O	$-CH_2-$	pyridin-4-ylmethyl
3	N	C	C	C	O	$-CH_2-$	4-fluorophenyl
4	N	C	C	C	O	$-CH_2-$	4-methoxy-phenyl

Table 3:

Exemplified intermediates of general formula VIII

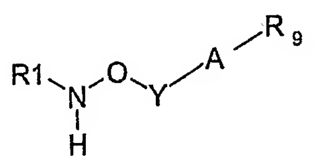


[VIII]

Preparation	D	E	F	G	X	B-R_8
5	N	C	C	C	$-CH_2-$	pyridin-4-ylmethyl
6	N	C	C	C	$-CH_2-$	4-fluorophenyl
7	N	C	C	C	$-CH_2-$	4-methoxy-phenyl

Table 4:

Exemplified O-substituted (Y-A) hydroxylamines of general formula III



[III]

Preparation	R1	Y	A-R_9
8	H	$-CH_2-$	3,4,5-tri-methoxyphenyl
9	H	$-CH_2-$	4-chlorophenyl
10	H	$-CH_2-$	4-cyanophenyl
11	H	$-CH_2-$	quinolin-2-yl
12	H	$-CH_2-$	2-methylthiazol-4-yl

General Procedure 1: Synthesis of hydroxamic acid esters of general formula (I) from carboxylic acids of general formula (II).

A carboxylic acid of general formula (II) (1.0 e.q.) was dissolved in dry DMF or dry NMP under argon to obtain a 0.2M solution or suspension. N,N'-Carbonyldiimidazole (1.0 e.q.) was added in one portion and the resulting reaction mixture was stirred at room temperature for 45-60 min. O-Substituted hydroxylamine (III) or the corresponding hydrochloride (1.0 e.q.) was added and stirring continued at room temperature for 20 hours. Water was added and if the product precipitated, it was isolated by filtration and recrystallised (typically from ethanol). If the crude product did not precipitate as a solid material, the mixture was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was either purified by crystallisation or chromatography on silica gel (EtOAc/petroleum ether) to afford hydroxamic acid esters of general formula (I).

General Procedure 2: Synthesis of carboxylic acids of general formula (II) from the corresponding esters of general formula (VII).

To a stirred 0.25 M solution of ester with the general formula (VII) (1.0 e.q.) in THF/water (3:1, v/v) was added lithium hydroxide (6-8 e.q.). The reaction mixture was stirred at room temperature for 60 min. then heated to 60°C and stirring continued at this temperature for 20 hours. The mixture was cooled to room temperature and most of the THF solvent was evaporated under reduced pressure. The residue was diluted with water and the pH of the mixture was adjusted to 5-6 by addition of 4 M hydrochloric acid. The resulting precipitated

material was isolated by filtration and washed with water. Crystallisation from ethanol afforded the carboxylic acid of general formula (II).

General procedure 3: Synthesis of carboxylic acids of general formula (II) from the corresponding nitriles of general formula (VIII).

A suspension of nitrile of general formula (VIII) in 27.65% sodium hydroxide (2.5 ml/mmol nitrile) and methanol (1 ml/mmol of nitrile) was heated to reflux and stirred at this temperature for 3 hours. The mixture was cooled to room temperature and diluted with water. The pH of the mixture was adjusted to 5-6 by addition of 4M hydrochloric acid. If a precipitate formed, it was isolated by filtration washed with water and dried under high vacuum, affording carboxylic acid of general formula (II). If the product acid did not precipitate the neutralised aqueous mixture was concentrated under reduced pressure and extracted thoroughly with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from ethanol or methanol and gave the carboxylic acid of general formula (II).

Preparation 1: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid.

General procedure 2. (alternative preparation is described in WO 00/27819)

Starting material: 2-[(pyridin-4-ylmethyl)-amino]-benzoic acid methyl ester (Manley P.W. *et al. J. Med. Chem.* (2002), 45, 5687-5693).

^{13}C-NMR (DMSO-d_6) δ 169.69, 150.05, 149.35, 148.64, 134.03, 131.47, 121.70, 114.54, 111.30, 110.45, 44.41.

Preparation 2: 2-[(pyridin-4-ylmethyl)-amino]-nicotinic acid

General procedure 3.

Starting material: 2-[(Pyridin-4-ylmethyl-amino]-nicotinonitrile (see preparation 5).

^{13}C-NMR (DMSO-d_6) δ 168.75, 157.91, 153.01, 149.64, 149.27, 140.13, 121.94, 111.67, 106.50, 42.69.

Preparation 3: 2-(4-Fluoro-benzylamino)-nicotinic acid

General procedure 3.

Starting material: 2-(4-Fluoro-benzylamino)-nicotinonitrile (see preparation 6).

^{1}H-NMR (DMSO-d_6) δ 13.07 (bs, 1H), 8.47 (bs, 1H), 8.25 (dd, 1H), 8.10 (dd, 1H), 7.34-7.39 (m, 2H), 7.10-7.16 (m, 2H), 6.63 (dd, 1H), 4.67 (d, 2H).

Preparation 4: 2-(4-Methoxy-benzylamino)-nicotinic acid

General procedure 3.
Starting material: 2-(4-Methoxy-benzylamino)-nicotinonitrile (see preparation 7).
^{13}C-NMR (DMSO-d_6) δ 168.83, 158.11, 157.96, 153.19, 140.06, 131.74, 128.55, 113.69, 111.21, 105.95, 54.92, 43.16.

Preparation 5: 2-[(Pyridin-4-ylmethyl-amino]-nicotinonitrile

To a stirred solution of 2-chloro-nicotinonitrile (Aldrich, 10.4 g, 75.06 mmol) in dry NMP (40 ml) was added 4-(aminomethyl)pyridin (15.2 ml, 150.26 mmol). The reaction mixture was heated to 130°C, and stirred at this temperature for 20 hours. The mixture was cooled to room temperature and diluted with EtOAc (500 ml) and washed with saturated aqueous $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The remaining red-brown solid material was recrystallised from ethanol affording the title compound (7.73 g) as an off-white solid. The filtrate was evaporated under reduced pressure, redissolved in 2% methanol/EtOAc (v/v) and filtrated through a pad of silica gel. The filtrate was evaporated under reduced pressure and the residue was recrystallised from ethanol and gave an additional amount of the title compound (2.44 g).
^{13}C-NMR (DMSO-d_6) δ 157.80, 152.65, 149.30, 149.10, 142.49, 121.94, 116.65, 112.09, 90.62, 43.00.

Preparation 6: 2-(4-Fluoro-benzylamino)-nicotinonitrile

To a stirred suspension of 2-chloro-nicotinonitrile (Aldrich, 3.30 g, 23.82 mmol) in 2-propanol (30 ml) was added 4-fluoro-benzylamine (3.00 ml, 26.25 mmol) and N,N-diisopropylethylamine (8.30 ml, 47.65 mmol). The reaction mixture was heated to 80°C for 24 hours. More 4-fluoro-benzylamine (0.55 ml, 4.81 mmol) was added and stirring was continued at 80°C for another 24 hours. The reaction mixture was cooled to room temperature and the precipitated material was isolated by filtration and washed with 2-propanol. Residual 2-propanol was removed *in vacuo* affording the title compound (3.04 g) as a white crystalline material.
^{1}H-NMR (DMSO-d_6) δ 8.23-8.25 (m, 1H), 7.91 (dd, 1H), 7.73 (t, 1H), 7.34-7.38 (m, 2H), 7.08-7.14 (m, 2H), 6.63-6.67 (m, 1H), 4.57 (d, 2H).

Preparation 7: 2-(4-Methoxy-benzylamino)-nicotinonitrile

To a stirred mixture of 2-chloro-nicotinonitrile (Aldrich, 2.20 g, 15.88 mmol) and 4-methoxy-benzylamine (2.27 ml, 17.49 mmol) in 2-propanol (20 ml) was added N,N-diisopropylethylamine (5.53 ml, 31.75 mmol). The reaction mixture was heated to 80°C and stirred at this temperature for 24 hours. More 4-methoxy-benzylamine (0.50 ml, 3.85

mmol) was added and stirring continued at 70°C for 48 hours. The mixture was cooled to room temperature and the resulting solid material (4-methoxy-benzylamine hydrochloride) removed by filtration. On standing a crystalline product formed in the filtrate, which was isolated by filtration, washed with 2-propanol and dried under reduced pressure affording the title compound as pale yellow crystals (1.27 g).

^{1}H-NMR (DMSO-d_6) δ 8.21-8.30 (m, 1H), 7.90 (d, 1H), 7.65 (t, 1H), 7.25 (d, 2H), 6.85 (d, 2H), 6.59-6.68 (m, 1H), 4.50 (d, 2H), 3.75 (s, 3H).

Preparation 8: O-(3,4,5-Trimethoxy-benzyl)-hydroxylamine hydrochloride

To a stirred solution of 3,4,5-trimethoxybenzyl chloride (1.00 g, 4.6 mmol) and *tert*-butyl-N-hydroxycarbamate (0.62g, 4.6 mmol) in acetonitrile (20 ml) was added $CsCO_3$ (4.51 g, 13.8 mmol). The reaction mixture was stirred at room temperature for 24 hours. Water was added and the products extracted twice with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by chromatography on silica using a gradient of EtOAc in petroleum ether (0-40%, v/v) affording 411 mg of Boc-protected O-(3,4,5-trimethoxy-benzyl)-hydroxylamine. This intermediate (383 mg/1.22 mmol) was treated with 37% hydrochloric acid (2.5 ml) in EtOAc (7.5 ml) for 30 min. at room temperature. The mixture was concentrated under reduced pressure and diethyl ether was added. The resulting precipitated material was isolated by filtration and dried under high vacuum affording the title compound (211 mg) as white shiny crystals.

^{1}H-NMR (DMSO-d_6) δ 11.10 (bs, 3H), 6.76 (s, 2H), 4.98 (s, 2H), 3.79 (s, 6H), 3.67 (s, 3H).

Preparation 9: O-(4-Chloro-benzyl)-hydroxylamine hydrochloride

Same procedure as described for preparation 8. Starting materials: 4-Chlorobenzyl bromide and *tert*-butyl-N-hydroxycarbamate.

^{1}H-NMR (DMSO-d_6) δ 11.18 (bs, 3H), 7.44-7.51 (m, 4H), 5.06 (s, 2H).

Preparation 10: O-(4-cyanobenzyl)hydroxylamine hydrochloride

N-Hydroxyphthalimide (3.30g, 20.2mmol) was dissolved in NMP (50 ml) and 4-cyanobenzyl bromide (4.35 g, 22.2 mmol) was added followed by drop-wise addition of 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) (3.0 ml, 20.1 mmol). After complete addition of DBU (ca. 15 min.) the reaction mixture was stirred at room temperature for 65 min. The mixture was poured into ice cooled 1M aqueous hydrochloric acid (500 ml) and the precipitated material was collected by filtration and washed with water and dried under high vacuum. This phthalimide derivative (5.31 g, 19.1 mmol) was suspended in ethanol (40 ml) and a solution of hydrazine hydrate (0.93 ml, 19.1 mmol) in ethanol (10 ml) was added drop

wise. The reaction mixture was heated to reflux and stirred for 2.5 hours. The mixture was cooled to room temperature and the solid material removed by filtration and washed with ethanol. The combined filtrates were evaporated under reduced pressure. The residue was resuspended in EtOAc and the undissolved material was removed by filtration. The EtOAc filtrate was washed with saturated aqueous $NaHCO_3$, and water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was suspended in diethyl ether (150 ml) and concentrated hydrochloric acid (50 ml) was added and the resulting slurry was stirred at room temperature for 30 min. The precipitated product was isolated by filtration, washed with diethyl ether and dried *in vacuo*, affording the title compound (2.24 g) as a white powder.

^{1}H-NMR (DMSO-d_6) δ 11.26 (bs, 3H), 7.90 (d, 2H), 7.63 (d, 2H), 5.17 (s, 2H).

Preparation 11: O-Quinolin-2-ylmethyl-hydroxylamine

tert-Butyl-N-hydroxycarbamate (1.00 g, 7.51 mmol) was dissolved in DMF (25 ml) and the mixture was cooled in an ice bath. Sodium hydride (655 mg of a 55-65% dispersion in mineral oil) was added and after 20 min. 2-chloromethyl-quinolin hydrochloride (1.6 g, 7.50 mmol) was added portion wise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 20 hours. The reaction was quenched by addition of water and the product was extracted with EtOAc. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was decanted with petroleum spirit and the product was crystallised from EtOAc/petroleum spirit, affording N-Boc protected O-Quinolin-2-ylmethyl-hydroxylamine (881 mg) as a pale yellow solid.^{13}C-NMR (DMSO-d_6) δ 157.12, 156.19, 146.78, 136.44, 129.60, 128.53, 127.78, 127.18, 126.48, 120.31, 79.81, 78.38, 27.89. This material (860 mg, 3.14 mmol) was dissolved in CH_2Cl_2 (10 ml) and trifluoroacetic acid (4.4 ml) was added. The reaction mixture was stirred at room temperature for 60 min. and the solvents were evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated under reduced pressure. This gave the title compound (376 mg) as a yellow oil, which was used without further purification.

Preparation 12: O-(2-Methyl-thiazol-4-ylmethyl)-hydroxylamine hydrochloride

N-Hydroxyphthalimide (15.2 g) was dissolved in DMF (120 ml) and 4-chloromethyl-2-methyl-thiazole (18.4 g) was added. The mixture was cooled in an ice bath and a solution of triethylamine (28.6 ml) in DMF (30 ml) was added drop wise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 3 days. The mixture was poured into water (600 ml) and the precipitated material was isolated by filtration

washed with water and dried *in vacuo*. This phthalimide intermediate (21.4 g) was refluxed in ethanol (150 ml) containing *n*-butylamine (7.7 ml) for 2.5 hours. The mixture was cooled to room temperature and 4M hydrochloric acid in diethyl ether (25 ml) was added. The mixture was placed at 0-5°C over night at the resulting precipitated material was isolated by filtration and washed with cold ethanol and diethyl ether, affording the title compound (11.2 g) as a white crystalline material.
^{13}C-NMR (DMSO-d_6) δ 166.85, 147.15, 121.35, 70.03, 18.37.

Example 1: N-Benzyloxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 1)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-benzylhydroxylamine hydrochloride (Aldrich).
^{13}C-NMR (DMSO-d_6) δ 166.9,149.7,149.1,148.3,136.1,132.5,129.0,128.4,128.3,128.2, 122.1,114.9,113.6,111.6,76.9,44.9.

Example 2: N-(4-Nitro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 2)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(4-nitrobenzyl)hydroxylamine hydrochloride (Aldrich).
^{1}H-NMR (DMSO-d_6) δ 11.69 (bs,1H),8.49 (d,2H),8.26 (d,2H),7.89 (bt,1H), 7.77 (d,2H), 7.38 (d,1H),7.30 (d,2H),7.20 (t,1H), 6.55 (t,1H),6.51 (d,1H),5.10 (s,2H),4.46 (d,1H).

Example 3: N-(2-Nitro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 3)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-nitrobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).
^{13}C-NMR (DMSO-d_6) δ 167.5,149.5,148.9,148.3,147.8,133.7,132.6,131.6,130.4,129.3, 128.1,124.6,122.0,114.8,113.0,111.5,73.2,44.8.

Example 4:2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethyl-benzyloxy)-benzamide (compound 4)

General procedure 1.
Starting materials: 2-[(Pyridine-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and

O-(3-trifluoromethylbenzyl)hydroxylamine hydrochloride (Bionet research intermediates). ^{13}C-NMR (DMSO-d_6) δ 167.3,149.5 ,149.0,148.3,137.5 ,132.7,132.6,129.3,129.0,128.0, 125.1,124.8,124.1,122.0,114.8,113.3,111.5,76.0,44.8.

Example 5: 2-[(Pyridin-4-ylmethyl)-amino]-N-(2-trifluoromethyl-benzyloxy)-benzamide (compound 5)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-trifluoromethylbenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.5,149.5,149.0,148.3,134.3,132.6,132.5, 131.1,128.7 ,128.1, 126.9,125.6,124.2,122.0,114.8,113.1,111.5,72.7,44.8.

Example 6: N2-[(Pyridin-4-ylmethyl)-amino]-N-(4-trifluoromethyl-benzyloxy)-benzamide (compound 6)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(4-trifluoromethylbenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.4,149.6,149.0,148.3,140.9,132.6,129.2, 128.6,128.1 ,125.1, 124.2,122.0,114.8,113.2, 111.5,76.0,44.8.

Example 7: N-(4-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 7)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(4-methoxybenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.1,159.3,149.5,149.0,148.3,132.4,130.6, 128.0,127.8,122.0, 114.8,113.6,113.5,111.4,76.6,55.0,44.8.

Example 8: N-(3-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 8)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3-methoxybenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.1,159.1,149.5,149.0,148.3,137.5,132.4, 129.3,128.0,122.0, 120.8,114.8,114.0,113.7, 113.4,111.4,76.7,54.9,44.8.

Example 9: 2-[(pyridin-4-ylmethyl)-amino]-N-(3,4,5-trimethoxy-benzyloxy)-benzamide (compound 9)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3,4,5-trimethoxybenzyl)hydroxylamine hydrochloride (Se preparation 8).

^{13}C-NMR (DMSO-d_6) δ 167.1,152.7,149.5,149.0,148.2,137.3,132.5, 131.6,128.1,121.9, 114.8,113.5,111.4,105.9, 76.9,59.9,55.8,44.8

Example 10: N-(4-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 10)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(4-chlorobenzyl)hydroxylamine hydrochloride (see preparation 9).

^{13}C-NMR (DMSO-d_6) δ 167.2,149.5,149.0,148.3,135.0,132.8,132.5, 130.7,128.2,128.0, 122.0,114.8,113.3,111.5, 76.0,44.8.

Example 11: N-(3-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 11)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3-chlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,149.8,149.5,149.0,148.3,138.6,132.9, 132.5,130.1,128.4, 128.1,127.2,122.0,114.8,113.3,111.5,76.0,44.8.

Example 12: N-(2-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 12)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-chlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,149.5,149.0,148.3,133.5,133.1,132.5, 131.3,130.0,129.2, 128.1,127.1,122.0,114.8, 113.3,111.4,73.7,44.8.

Example 13: N-(2-Bromo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 13)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-bromobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.4,149.5,149.0,148.3,135.3,132.5,132.4, 131.1,130.2,128.2,127.7,123.2,122.0,114.8, 113.2,111.4,75.9,44.8.

Example 14: N-(2,4-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 14)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2,4-dichlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.4,149.5,148.9,148.3,134.2,133.7,132.8, 132.6,128.7,128.1, 127.3,121.9,114.8,113.2, 111.4,73.0,44.8.

Example 15: N-(3,4-Dichloro-benzyloxy)-2-[(pyridine-4-ylmethyl)-amino]-benzamide (compound 15)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3,4-dichlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,149.5,148.9,148.3,137.4,132.6,130.9, 130.7,130.5,130.4, 128.9,128.1,121.9,114.8, 113.2,111.5,75.3,44.8.

Example 16: N-(2,6-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 16)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2,6-dichlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,149.5,149.0,148.3,136.7,132.4,131.5, 131.3,128.5,128.3, 121.9,114.7,113.4,111.3, 70.7,44.8.

Example 17: N-(3,5-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 17)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3,5-dichlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.4,149.5,148.9,148.3,140.6,133.8,132.6, 128.0,127.6,127.1, 121.9,114.8,113.2,111.5, 75.3,44.8.

Example 18: N-(2,3-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 18)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2,3-dichlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,149.5,148.9,148.3,136.3,132.6,131.7, 131.1,130.3,129.7, 128.1,128.0,121.9,114.8, 113.2,111.4,74.1,44.8.

Example 19: N-(2,5-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 19)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2,5-dichlorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.4,149.5,148.9,148.3,135.9,132.5,131.7, 131.5,130.8,130.4, 129.6,128.1,121.9,114.8,113.1,111.5,73.1,44.8.

Example 20: N-(2-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 20)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-fluorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.2,160.8,149.5,149.0,148.3,132.0,130.7, 128.1,124.3,122.8, 122.0,115.4,115.1,114.8,113.3,111.4,70.2,44.8.

Example 21: N-(3-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 21)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3-fluorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,162.0,149.5,148.9,148.3,138.9,132.5, 130.2,128.0,124.5, 122.0,115.3,114.9,114.7,113.3,111.5,76.0,44.8.

Example 22: N-(4-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 22)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(4-fluorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.2,162.0,149.5,149.0,148.3,132.5,132.2, 131.1,128.0,122.0, 115.2,114.8,113.3,111.5,76.1,44.8.

Example 23: N-(2-Chloro-6-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 23)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-chloro-6-fluorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,162.0,149.5,149.0,148.3,135.9,132.4, 131.7,128.1,125.4, 121.9,121.7,114.7,114.5, 113.3,111.4,66.9,44.7.

Example 24: N-(2-Chloro-4-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 24)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-chloro-4-fluorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,161.8,149.5,149.0,148.3,134.3,133.1, 132.5,130.1,128.1, 122.0,116.5,114.8,114.3,113.2,111.5,73.0,44.8.

Example 25: N-(3-Chloro-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 25)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3-chloro-2-fluorobenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.2,156.0,149.5,148.9,148.3,132.5,130.9, 130.8,128.0,125.2, 124.9,121.9,119.5,114.8,113.2,111.4,70.2,44.7.

Example 26: 4-{2-[(pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid methyl ester (compound 26)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and 4-aminooxymethyl-benzoic acid methyl ester hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 167.3,166.0,149.5,148.9,148.3,141.5,132.5, 129.3,129.1,128.7, 128.1,122.0,114.8,113.2,111.5,76.2,52.1,44.8.

Example 27: N-(4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 27)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(4-cyanobenzyl)hydroxylamine hydrochloride (see preparation 10).
^{13}C-NMR (DMSO-d_6) δ 167.4,149.6,148.9,148.3,141.8,132.6,132.2, 129.1,128.1,122.0, 118.7,114.8,113.1,111.5, 110.8,75.9,44.8.

Example 28: 2-[(Pyridin-4-ylmethyl)-amino]-N-(quinolin-2-ylmethoxy)-benzamide (compound 28)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-Quinolin-2-ylmethyl-hydroxylamine (see preparation 11).
^{13}C-NMR (DMSO-d_6) δ 156.9,149.5,148.9,148.2,146.8,136.6,132.5, 129.6,128.6 ,128.1, 127.8,127.3,126.6,121.9,120.6,114.8,113.2,111.4,78.3,44.8.

Example 29: N-Phenoxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 29)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-phenylhydroxylamine hydrochloride (Fluka).
^{13}C-NMR (DMSO-d_6) δ 159.7,149.6,148.8,148.6,133.1,129.4,128.3, 122.2,122.0,114.9, 112.9,112.1,111.7,44.8.

Example 30: N-(2-Phenoxy-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 30)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-phenoxyethyl)-hydroxylamine hydrochloride (Bionet research intermediates).
^{13}C-NMR (DMSO-d_6) δ 167.5,158.5,149.8,149.2,148.6,132.8,129.6, 128.3,122.2,120.8, 115.0,114.6,113.4,111.7, 74.0,65.7,45.0.

Example 31: N-(3-Phenyl-propoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 31)

General procedure 1.
Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(3-phenylpropyl)hydroxylamine hydrochloride (SPECS).
^{13}C-NMR (DMSO-d_6) δ 167.1,149.5,149.0,148.3,141.6,132.4,128.3, 128.2,128.0,125.7, 122.0,114.8,113.5,111.5,74.5,44.8,31.4,29.6.

Example 32: N-(2-methyl-thiazol-4 ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 32)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-benzoic acid (see preparation 1) and O-(2-Methyl-thiazol-4-ylmethyl)-hydroxylamine hydrochloride (see preparation 12).

^{13}C-NMR (DMSO-d_6) δ 167.1, 165.3, 150.5, 149.5, 148.9, 148.3, 132.5, 128.1, 122.0, 119.0, 114.8, 113.4, 111.4, 71.9, 55.9, 44.8, 18.6.

Example 33:N-Benzyloxy-2-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide (compound 33)

General procedure 1.

Starting materials: 2-[(Pyridin-4-ylmethyl)-amino]-nicotinic acid (see preparation 2) and O-benzylhydroxylamine hydrochloride (Aldrich).

^{13}C-NMR (DMSO-d_6) δ 156.7,151.2,149.7,149.4,136.2,136.0,129.0, 128.3,122.1,111.2, 108.4,77.0,42.8.

Example 34: 2-(4-Fluoro-benzylamino)-N-(4-methoxy-benzyloxy)-nicotinamide (compound 34)

General procedure 1.

Starting materials: 2-(4-Fluoro-benzylamino)-nicotinic acid (see preparation 3) and O-(4-methoxybenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 165.7,161.0,159.3,156.7,151.2,136.4,136.0, 130.6,129.1,127.8, 114.9,113.6,113.5,110.8, 108.0,76.6,55.0,43.0.

Example 35: 2-(4-methoxy-benzylamino)-N-(4-methoxy-benzyloxy)-nicotinamide (compound 35)

General procedure 1.

Starting materials: 2-(4-Methoxy-benzylamino)-nicotinic acid (see preparation 4) and O-(4-methoxybenzyl)hydroxylamine hydrochloride (Bionet research intermediates).

^{13}C-NMR (DMSO-d_6) δ 165.8,159.3,158.1,156.8,151.2,135.9,131.9, 130.6,128.6,127.7, 113.7,113.6,110.6,107.7, 76.6,55.0,54.9,43.3.

Example 36: *In vitro* KDR kinase assay

The intracellular domain of the KDR receptor was used in the *in vitro* KDR assay. This domain contains the tyrosine kinase domain of KDR, and when expressed in Sf9 cells, this domain is constitutively active i.e. the kinase domain is phosphorylated on tyrosine residues. The substrate is the two SH2 domains of PLCγ, which has been shown to be

sufficient for physiological interaction with PDGF-R (Ji, Q.s., Chattopadhyay, A., Vecchi, M., and Carpenter, G. *Mol.Cell.Biol., 19*: 4961-4970, *1999*) and TrkA (Angeles, T.S., Steffler, C., Bartlett, B.A., Hudkins, R.L., Stephens, R.M., Kaplan, D.R., and Dionne, C.A. *Anal Biochem*, *236*: 49-55, *1996*).

Biological materials:

Antibodies against PLCγ1 (530) (sc-426), Flk-1/KDR (C-20) (sc-315), GST (B-14) (sc-138) were purchased form Santa Cruz Biotechnology Inc., Santa-Cruz-Europe, Heidelberg, Germany. Anti-phospho-Tyrosine (4G10) (cat. no. 05-321) was from Upstate Biotechnology. Anti-phospho-Tyrosine (PY20) (cat. no. P11120) was from Transduction Laboratories, BD Biosciences, Franklin Lakes, NJ, USA. Europium-labelled PY20 anti-phosphotyrosine antibody was from Wallac, Finland. Gluthathione Sepharose 4B (cat. no. 17-0756-01), ECL Western Blotting detection reagent (cat. no.2106), ECL Hyperfilm (cat. no. RPN 3103H), 14.3-220 kDa rainbow coloured protein molecular markers (cat. no. RPN 756), PD-10 columns, γ-^{32}P-ATP (cat. no. AA0068 250 μCi/25μl), pGEX-4T-1 vector and BL21 *E. Coli* cells (cat. no. 27-1542-01) were purchased from Amersham-Pharmacia Biotech, Europe, Denmark. Pefabloc (cat. no. 1429868), Leupeptin (cat. no. 1017101), Aprotinin (cat. no. 236624) were from Roche Molecular Biochemical, Hvidovre, Denmark. Secondary antibodies were from DAKO, Glostrup, Denmark. Biotin-marker (cat. no. 7726L) was from Cell Signaling Technologies Inc.,Beverly, MA, USA. Non-fat milk (MILEX®240) was from Arla (former MD Foods), Viby, Denmark. Nitro-cellulose membrane 0.2 μm (cat. no. A010A304C) was from Advantec MFC. 3MM Whatmann filters (cat. no. 3030917) was from Whatmann International, England. TRIzol™, TA- cloning kit, GATEWAY system, pDONR201 Entry vector, pDEST20 vector, Bac-to-Bac system , pCR-3.1-Uni vector, pCR-Blunt II-TOPO, Zero Blunt TOPO cloning kit, Sf9 cell line, Grace's insect Medium Supplemented and CELLFECTIN were from Invitrogen, Carlsbad, CA, USA. DMSO (D-2650), Gluthathione (G-4251), Lysozyme (L-6876) and 10×PBS were purchased from Sigma, Vallensbæk Str. Denmark. Chemicals for the different buffers were from Merck KGaA, Darmstadt, Germany. Black 96-wells microtiter MaxiSorp plates were from NUNC, Denmark.

RT-PCR cloning of human KDR:

Total RNA was isolated from human umbilical vein endothelial (HUVE) cells using TRIzol™ reagent according to the manufacturer's protocol. Two μg of total RNA was reverse transcribed into the first-strand cDNA using oligo(dT)$_{16}$ as a primer. The first-strand cDNA, encoding the complete coding region of human KDR, was then PCR amplified using the oligonucleotides 5'-TCTAGACAGGCGCTGGGA-GAAAGA-3' and 5'-TGCTGGTGGAAAGAACAA-CACTTCA-3'. The design of the oligonucleotides was based on the DNA sequence from

GenBank accesssion no. X89776 and X61656. The PCR product was cloned into the pCR-3.1-Uni expression vector using the TA-cloning kit according to the manufacturer's protocol. The plasmid was designated pMWM-78.

Construction of KDR-cyt baculovirus bacmid:
The cDNA encoding the intracellular part of KDR (KDR-cyt) including the kinase domain (nucleotide 2683-4455, transcriptional start being +1) was PCR amplified using the oligonucleotides 5'-GGGGACAAGTTTGTACAAAAAAGCAGGCTCCGGAG-GGGAACTGAAGACGGGCTACT-3' and 5'-GGGGACCACTTTGTACAAGA-AAGCTGGGTATTTGCTGGTGGAAAGAACAACACTT-3'. Both oligonucleotides contained attB recombination sequences (underlined) for further cloning by the GATEWAY system. The PCR product was subcloned into the pDONR201 Entry vector using the GATEWAY system according to the manufacturer's protocol. The identity of the sequence was verified by DNA sequencing. The cDNA encoding the KDR-cyt was then transferred from the pDORN201 to the pDEST20 vector thereby placing the KDR-cyt in a cassette for insect cell expression of a GST-KDR-cyt fusion protein under control of the polyhedrin promoter. The GST-KDR-cyt was transferred to a baculovirus bacmid using the Bac-to-Bac system according to the manufacturer´s protocol. Briefly, the pDEST20/KDR-cyt was transformed into *E. coli* DH10Bac in which it recombined with the bMON14272 bacmid. The recombined bacmid was purified from the E.coli by miniprep.

Sf9 cells:
The Sf9 cell line originating from the pupal ovarian tissue of the fall army worm, *Spodoptera frugiperda* was grown in Grace's Insect Medium Supplemented, 10% fetal calf serum (FCS), 100 U/ml penicillin and 100 mg/ml streptomycin at 27°C. The cell line was passaged at confluency and typically diluted at 1:6. Cells were dislodged by scraping.

Production of GST-KDR-cyt baculovirus in Sf9 cells:
The baculovirus bacmid containing the GST-KDR-cyt expression cassette was transfected into Sf9 insect cells using CELLFECTIN liposome mediated transfection according to the manufaturer's protocol. Three days after transfection the medium was collected and clarified by centrifugation (500xG, 5 minutes, 4°C) and the supernatant containing the baculovirus particles was placed at 4°C for short term storage or at -80°C for long term storage.

Amplification of recombinant baculovirus:

In order to amplify the virus, Sf9 cells from a subconfluent culture were seeded in a T-80 culture flask at a density of $1x10^5$ cells/cm^2 and left to adhere for 45-60 min. at 27°C. The medium was aspired from the monolayer and a 300 µl virus stock from the first production was added together with 1700 µl Grace's Insect Medium Supplemented (no antibiotics and no FCS). The cells were incubated for 1 hour at 27°C before the addition of 15 ml of Grace's Insect Medium Supplemented (100 U/ml penicillin, 100 mg/ml streptomycin and 10% FCS). Following an incubation period of 72 hours, the supernatant containing the baculovirus was harvested as described above.

Production of GST-KDR-cyt fusion protein:
For the purification GST coupled KDR-cyt from Sf-9 cells, 2 T-175 culture flasks were seeded with cells from a subconfluent culture at a density of $1x10^5$ cells/cm^2. The cells were left to adhere at 27°C for 45-60 min. The culture medium was removed and cells were infected with an optimal amount of virus in 20 ml Grace's Insect Medium Supplemented (no antibiotics and no FCS). Following an incubation period of 60 min. at 27°C, 17 ml Grace's Insect Medium Supplemented (10% FCS, 100U/ml penicillin and 100mg/ml streptomycin) was added and the cells were harvested at the optimal time after infection. The cells were scraped off into the medium in their culture flask, and the cells and medium was transferred to tubes and centrifuged (500×G, 5 min., 4°C). The supernatant was aspired and the pellet was washed in 2x5 ml ice cold 1× phosphate buffered saline (PBS). The cells were lysed in 4 ml of the following lysis buffer which was prepared just prior to use: 50 mM HEPES pH 7.5, 150 mM NaCl, 10 mM EDTA, 10 mM Na_4PO_7,100 mM NaF, 500 µM Pefabloc, 10 µg/µl Aprotinin, 10 µg/µl Leupeptin, 2 mM Na_3VO_4 and 1% Triton X-100. The sample was incubated on ice for 10 min., then centrifuged (10.000×G, 10 min., 4°C) and the supernatant was transferred to a new centrifuge tube.

Purification of GST-KDR-cyt fusion protein:
Glutathione-Sepharose beads were prepared by washing 400 µl beads 3 times with a HNT buffer containing 30mM HEPES pH 7.5, 30mM NaCl and 0.1% Triton X-100 followed by washing twice in the lysis buffer (50 mM HEPES pH 7.5, 150 mM NaCl, 10 mM EDTA, 10 mM Na_4PO_7,100 mM NaF, 500 µM Pefabloc, 10 µg/µl Aprotinin, 10 µg/µl Leupeptin, 2 mM Na_3VO_4 and 1% Triton X-100. Then 4000 µl supernatant from the lysed cells were added to the Glutathione-Sepharose beads and the sample was left to rotate slowly for 2 hours at 4°C after which it was centrifuged (1000×G, 30 sec., 4°C) and the supernatant removed.
To elute the proteins, 400 µl 50 mM Tris/HCl pH 8.0 and 20 mM Gluthathione were added to the sample, which was incubated for 20 min. while rotating slowly at 4°C. The sample was centrifuged (1000×G, 30 sec., 4°C) and the supernatant was collected. This procedure

was repeated 4 times or till no more protein was eluted determined by measuring the absorbance at 280nm (A_{280}). The GST-KDR-cyt was desalted, and the Glutathione/Tris buffer was exchanged to a TBS-Buffer (150 mM NaCl, 10 mM Tris/HCl pH 7.5) using a PD10 column. The PD10 column contains Sephadex G-25 M. Briefly, the GST-KDR-cyt eluate was added to the PD-10 column, and eluted with 2.5 ml TBS-Buffer. The GST-KDR-cyt eluate in the TBS-Buffer was measured by A_{280}, and the amount of protein was determined using a BSA standard. The purified GST-protein was analysed by SDS-PAGE followed by Coomasie staining and Western blotting.

RT-PCT cloning of human PLCγ cDNA:
Total RNA was isolated from human embryonic kidney HEK293 cells using TRIzol™ reagent. Two μg of total RNA was reverse transcribed into the first-strand cDNA using oligo$(dT)_{16}$ as a primer. The first-strand cDNA encoding a part of human PLCγ (nucleotide 1593-2635, GenBank accession no. M34667) containing the two SH2 domains and 2 tyrosine residues for phosphorylation, was then PCR amplified using the oligonucleotides 5'-TATCCCCACTACTTTGTTCTGACCA -3' and 5'-CACGGGGTTGACCATCTCTTC -3'. The PCR product was cloned into the pCR-Blunt II-TOPO vector using the Zero Blunt TOPO cloning kit according to the manufacturer's protocol. The cloned PLCγ was verified by DNA sequencing and the plasmid was designated pCR-Blunt II-TOPO/PLCγ.

Construction of GST-PLCγ vector for E.coli expression:
For the construction of the vector for *E. coli* expression of GST-PLCγ, the PLCγ part of the pCR-Blunt II-TOPO/PLCγ was PCR amplified using the oligonucleotides: 5'-ACGGAATTCAGCACAGAGCTGCAGTCCAATG-3' (incorporating an *Eco* RI site) and 5'-GATGCGGCCGCTCTTTGACTGCACACTTGAAAGTTGG-3' (incorporating a *Not* I site). This PCR product was then ligated into the pGEX-4T-1 vector using the *Eco* RI and *Not* I sites for expression of a GST-PLCγ fusion protein (see Figure 1). The construction was verified by DNA sequencing and designated pMWM-79.

Production of GST-PLCγ:
Escherichia coli BL21 cells were transformed with pGEX-PLCγ plasmid DNA. The bacteria were cultured to an OD_{600} of approx. 0.5 in a shaking incubator at 37°C, and induced by 1 mM isopropyl-β-D-thiogalactopyranoside (IPTG) for 4 hours. The bacteria were pelleted by centrifugation at 4000 rpm, for 20 min. at 4°C and the pellet was frozen at -80°C overnight. The following day, the pellet was resuspended in NETN-buffer (20 mM Tris-HCl pH 8.0, 10 mM NaCl, 1 mM EDTA, 500 μM Pefabloc, 10 μg/μl Leupeptin, 10 μg/μl Aprotinin, 0.5% Triton X-100, 10 mM DTT) on an ice-bath. The bacteria were lysed on ice-bath for 1 hour by the

addition of 20 μg/ml lysozyme, prior to centrifugation at 10.000×g, for 30 min. at 4°C, and transfer of the supernatant to new tubes.

Purification of GST-PLCγ:
Glutathione-Sepharose beads were prepared by washing 200 μl beads 3 times with a HNT buffer containing 30mM HEPES pH 7.5, 30mM NaCl and 0.1% Triton X-100 followed by washing twice in the NETN-buffer. Then the supernatant from the lysed bacteria was added to the Glutathione-Sepharose beads and the sample was left to rotate slowly for 2 hours at 4°C. The GST-PLCγ fusion protein adsorbed to the Glutathione-Sepharose beads was then washed three times in NETN-buffer and clarified by centrifugation at 1000×g, for 30 sec. at 4°C, to remove non-specifically bound proteins. Afterwards, the GST-PLCγ fusion proteins were separated from the beads by eluting with 200 μl elution-buffer (50 mM Tris-HCl pH 8.0, 20 mM Glutathione). The eluate was examined by an SDS-PAGE followed by Coomassie staining as well as by the Western blot technique using anti-PLCγ (530) (sc-426) (1:1000) and anti-GST (B-14) (sc-138) antibodies (1:2000). The yield of fusion protein was calculated from the absorbance at 280 nm.

The compounds to be tested were dissolved in DMSO at 10mM, stored at -20°C and protected from light. The maximum concentration of DMSO in the *in vitro* assay was 0.1%.Control samples received the same concentration of solvent as the samples treated with the test compounds.
For the kinase assays, black 96 wells MaxiSorp microtiter plates were coated by an overnight incubation with 100 μl / well of a 2.5 μg / ml solution of phospholipase Cγ in TBS buffer (40 mM Tris-HCl, pH 7.4, 20 mM $Mg(C_2H_3O_2)_2$, 0.02% NaN_3) at 4°C. The plates were washed 3 times with TBS buffer containing 0.1% Tween-20, and the residual binding sites were masked by incubation with 1% BSA in TBS buffer containing 0.1% Tween-20 for 1 h. The plates were washed again and the test compounds were added at final concentrations up to 10 μM, together with ATP at the final concentration of 100 μM in 50 μl TBS buffer / well. Then, 50 μl of the human intracellular domain of KDR (VEGF Receptor-2) finally diluted 3000-3500 fold were added and were incubated for 30 min at room temperature. The plates were washed and 100 μl of the Europium labelled PY-20 anti-phosphotyrosine antibody (Wallac, FIN) were incubated in each well at the concentration of approximately 114 ng / ml for 2 h. Then, the plates were washed and 100 μl of enhancer solution (Wallac, FIN) were incubated in each well for 5 min in the dark. The plates were read in a Victor^2 1420 multilabel counter, using a Europium protocol for time-resolved fluorometry (Wallac, FIN): excitation 340 nm, emission 615 nm, sample pulse cycle 400 μs. Fluorescence was measured for 400 μs between flashes after a delay time of 400 μs. The background

measured in the absence of enzyme was subtracted from all samples. The molar concentrations that inhibited 50% of the maximal enzymatic activity (IC_{50}) were calculated from the dose-response curve, by fitting a straight line between the two concentrations immediately above and below the 50% inhibition point (i.e. by solving the equation y=a+bx).

The *in vitro* KDR inhibitory activities of the compounds of general formula (I) of the present invention are listed in Table 5.

Table 5:

In vitro KDR inhibition

Compound No.	$-LogIC_{50}$ (KDR)
1	7.1
2	6.9
3	7.0
4	6.7
5	7.5
6	7.2
7	7.4
8	7.5
9	7.0
10	7.3
11	6.9
12	7.8
13	7.8
14	8.2
15	7.3
16	7.6
17	7.2
18	7.7
19	7.2
20	7.5
21	7.6
22	7.6
23	7.6
24	7.7

25	7.3
26	7.1
27	7.9
28	7.0
29	6.9
30	6.0
31	6.9
32	7.7
33	7.0
34	6.1
35	6.0

Example 37: Metabolic stability

Synthesis: The reference compounds 1 and 2 were prepared, using the methods described in WO 00/27819.

Isolation Procedure: Fresh rat (tac SPRD) hepatocytes were isolated by the end lobe technique. The right lateral liver lobe was cut off, placed on a perfusion platform and first perfused with calcium-free buffer, then buffer containing calcium and collagenase. The resulting cell suspension was centrifuged and the cells were washed several times.

Cell Viability and Yield: Cell viability and yield were assessed by the Trypan Blue Exclusion method. Only cell suspensions with viability over 80% were used. A suspension of 2 x 10^6 cells/mL was prepared and used for the assay.

Assay for Metabolic Stability: The test compounds (10 mM in DMSO) were placed in the liquid handler. A work-solution A (200 µM) was prepared by transferring 10 µL stock solution and 490 µL of a 0.2% solution of bovine serum albumin (BSA) in Krebs-Henseleit Buffer (KHB) to a microtiter plate. A work-solution B (10 µM) was prepared by transferring 25 µL of work-solution A and 475 µL KHB with 0.2% BSA to a microtiter plate. The cells were diluted to 2 x 10^6 cells/mL in KHB with 0.2% BSA, then 475 µL suspension was manually transferred to each well on two 24-well plates (Costar, cat. no. 3524). The plated cells were placed in the liquid handler and pre-incubated at 37 °C for 20 minutes in order to activate the metabolic capacity of the cells. After pre-incubation, 25 µL of work-solution B (10 µM) was added to each well, resulting in a final concentration of 0.5 µM test compound in the cell suspension. After addition of test compound to all wells on the plate, the plate was gently stirred and incubated. After 15, 30, 60, 90, and 120 minutes, 25 µL sample was withdrawn and added to a microtiter plate containing 100 µL methanol with

internal standard in order to stop the metabolic reaction. The microtiter plate was centrifuged (30 min, 4500 rpm) and the supernatant was analysed by LC-MS/MS (See Analysis for details). Samples t = 0 were made by manually adding 190 µL cell suspension to each well on a 96-well plate (Costar, cat. no. 3594; same material as the 24-well plates). 10 µL of work solution B was added to each well. After every four compounds (4 needles on the liquid handler), the plate was shaken, and 25 µL sample was instantly withdrawn and transferred to a microtiter plate containing 100 µL methanol with internal standard. The samples were analysed as described above.

Analysis: The HPLC system consisted of an Agilent 1100 Pump and Column Oven, and a CTC HTS-PAL AutoSampler. The mass spectrometer was a Sciex API 3000 MS/MS. The chromatographic conditions were as follows: Column: Zorbax Sb-C18, 5 µm, 2.1 x 50 mm; Injection volume:10 µL; Eluent A:5% methanol in MilliQ-water (v/v %), 2 mM ammonium acetate, 20 mM formic acid; Eluent B: 90% methanol in MilliQ-water (v/v %), 2 mM ammonium acetate, 20 mM formic acid; Flow rate: 500 µL/min; Step-gradient-program: 0-2 min, 0% B → 100% B; 2-3 min, 100% B; 3-3.1 min, 100% B → 0% B; 3.1-5 min, 0% B. Data were processed using Analyst version 1.2. All compounds were tuned and optimised on the mass spectrometer by infusion.

Calculations: The initial concentration of test compound was defined as 100%, and the amount of intact compound (%) versus time was plotted in a graph. The Area Under the Curve (AUC) was calculated using the linear trapezoidal method:

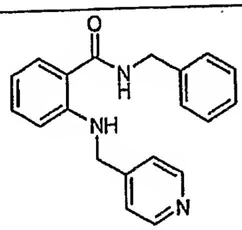
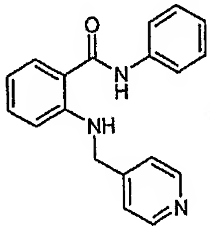
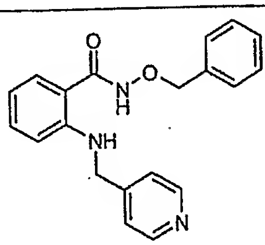
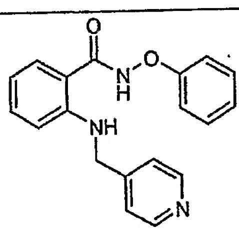
Linear trapezoidal rule: $$AUC_0^{t=2h} = \sum_{i=0}^{2h} (t_{i+1}-t_i) \times \frac{C_{i+1} - C_i}{2}$$

The AUC values for each compound were normalised to values between 0 and 100, and this number was used as a measurement for metabolic stability. Compounds with AUC values close to 0 have low metabolic stability, whereas compounds with AUC values close to 100 have high metabolic stability.

Table 6

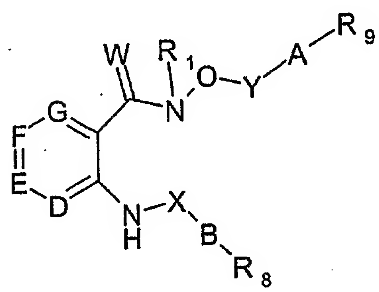
Metabolic stability of anthranilic acid amide derivatives of general structure A and of hydroxamic acid esters of general formula I:

Compound	AUC (norm.)

 Reference compound 1: Anthranilic acid amide according to WO WO/27819	10
 Reference compound 2: Anthranilic acid amide according to WO WO/27819	12
 Compound 1	16
 Compound 29	65

CLAIMS

1. A compound of general formula I



[I]

wherein R_1 represents hydrogen or a straight, branched and/or cyclic, saturated or unsaturated hydrocarbon radical, optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxyl, amino, nitro, and cyano;

D represents nitrogen or C-R_2;

E represents nitrogen or C-R_3;

F represents nitrogen or C-R_4;

G represents nitrogen or C-R_5;

R_2, R_3, R_4, and R_5 are the same or different and individually represent hydrogen, halogen, hydroxyl, amino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, or a straight or branched, saturated or unsaturated hydrocarbon radical, optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, amino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, and alkylcarbonylamino,
or R_2 and R_3, or R_3 and R_4, or R_4 and R_5 together with the C atoms to which they are attached form a 5- or 6-membered carbocyclic or heterocyclic ring;

W represents oxygen, sulphur, two hydrogen atoms, $=CH_2$, $=N\text{-}O\text{-}R_6$ or the group $=N(R_6)$;

R6 represents hydrogen, hydroxy, cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl, heteroaryl, alkenyl, alkynyl, or alkyl;

X and Y independently represents a radical of the formula $-(CH_2)_n-$, $-(CH_2)_p-CH=CH-(CH_2)_q-$, $-(CH_2)_r-O-(CH_2)_s$, $-(CH_2)_t-NH-(CH_2)_u$, $-(CH_2)_w-C(O)-NH-(CH_2)_z$ where n, p, q, r, s, t, u, w, and z are integers from 0-6, said radical may optionally be substituted by one or more substituents independently selected from the group consisting of R_7;

R_7 represents hydrogen, oxo, halogen, hydroxyl, amino, imino, nitro, carboxy, cyano, cycloalkyl, alkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkenyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, and alkylcarbonylamino, wherein said amino, imino, cycloalkyl, alkyl, aryl, heteroaryl, heterocycloalkyl, cycloalkenyl, alkenyl, alkynyl, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, aminocarbonyl, and alkylcarbonylamino is optionally substituted by one or more substituents independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, imino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, heterocycloalkyl, aryl, heteroaryl, and alkylaminocarbonyl;

B represents aryl, heteroaryl, heterocycloalkyl, cycloalkyl, or cycloalkenyl, all of which are optionally substituted with one or more substituents independently selected from the group consisting of R_8;

R_8 represents hydrogen, halogen, hydroxyl, amino, imino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, heterocycloalkyl, aryl or heteroaryl, alkylaminocarbonyl, and a straight or branched, saturated or unsaturated hydrocarbon radical, optionally substituted with one or more substituents independently selected from the group consisting of R_7;

A represents a straight, branched and/or cyclic, saturated or unsaturated hydrocarbon, a heterocycloalkyl, or a heteroaryl,
all of which are optionally substituted with one or more substituents independently selected from the group consisting of R_9;

R_9 represents hydrogen, oxo, halogen, hydroxyl, amino, nitro, carboxy, cyano, alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, formyl, aminocarbonyl, alkylcarbonylamino, alkylaminocarbonyl, heterocycloalkyl, heteroaryl and a straight or branched, saturated or unsaturated hydrocarbon radical,
wherein said straight or branched, saturated or unsaturated alkoxy, alkylthio, alkoxycarbonyl, alkylcarbonyloxy, alkoxycarbonyloxy, alkylcarbonyl, alkoxysulfonyloxy, aminosulfonyl, alkylsulfonylamino, aminocarbonyl, alkylcarbonylamino, or alkylaminocarbonyl, heterocycloalkyl, heteroaryl and straight or branched, saturated or unsaturated hydrocarbon radical is optionally substituted by one or more substituents independently selected from the group consisting of R_7;

and pharmaceutically acceptable salts, hydrates, or solvates thereof;

provided that the compound is not
2-[(2-chloro-4-iodophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-N-methyl-benzamide,
2-[(2,6-dichloro-3-methylphenyl)amino]-N-methoxy)-N-methyl-benzamide, or
2-[(2,6-dichlorophenyl)amino]-N-hydroxy-N-methyl-benzamide.

2. A compound according to claim 1 wherein W represents oxygen.

3. A compound according to claim 1-2 wherein R_1 represents hydrogen.

4. A compound according to claim 1-3 wherein D is C-R_2, E is C-R_3, F is C-R_4, and G is C-R_5.

5. A compound according to claim 1-4 wherein R_2, R_3, R_4, and R_5 are hydrogen.

6. A compound according to claim 1-3 wherein D is nitrogen, E is C-R_3, F is C-R_4, and G is C-R_5.

7. A compound according to claim 1-4 or 6 wherein R_3, R_4, and R_5 are hydrogen.

8. A compound according to claim 1-7 wherein B represents substituted or unsubstituted pyridyl, such as 2- pyridyl, 3- pyridyl, or 4-pyridyl.

9. A compound according to claim 1-7 wherein B represents substituted or unsubstituted phenyl.

10. A compound according to claim 1-9 wherein R_8 is hydrogen, chloro, bromo, fluoro, or methoxy.

11. A compound according to claim 1-10 wherein X is a bond, $-CH_2-$, or $-CH=CH-$.

12. A compound according to claim 1-11 wherein Y is radical of the formula $-(CH_2)_n-$, where n is an integer from 0-6; or Y is radical of the formula $-(CH_2)_p-C(O)-NH-(CH_2)_q$, where p is an integer from 0-6 and q is 0; or Y is radical of the formula $-(CH_2)_r-O-(CH_2)_s$, where r is an integer from 0-6 and s is 0.

13. A compound according to claim 1-11 wherein Y is a bond, $-CH_2-$, or $-CH(CH_3)-$, $-CH_2-CH_2-O-$, $-CH_2-CH_2-CH_2-$, $-CH_2-C(O)-$, or $-CH_2-C(O)-NH-$.

14. A compound according to claim 1-13 wherein A represents substituted or unsubstituted (C_6-C_{10})aryl, or substituted or unsubstituted (C_{3-10})heterocycloalkyl, or substituted or unsubstituted (C_2-C_{10})heteroaryl.

15. A compound according to claim 1-14 wherein A represents substituted or unsubstituted phenyl, substituted or unsubstituted (C_5)heteroaryl, or substituted or unsubstituted (C_9)heteroaryl.

16. A compound according to claim 1-15 wherein A represents substituted or unsubstituted phenyl, substituted or unsubstituted thiazol, or substituted or unsubstituted quinoline.

17. A compound according to claim 1-16 wherein R_9 is nitro, fluoro, chloro, bromo, methoxy, hydrogen, carbomethoxy, cyano, or methyl.

18. A compound according to claim 1-17 wherein $B-R_8$ represents 4-pyridyl, 4-fluorophenyl, or 4-methoxyphenyl.

19. A compound according to claim 1-18 wherein A-R_9 represents 2-nitrophenyl, 4-nitrophenyl, 3-trifluoromethylphenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-methoxyphenyl, 3,4,5-trimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 3,5-dichlorophenyl, 2,3-dichlorophenyl, 3,6-dichlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 6-fluoro-2-chlorophenyl, 4-fluoro-2-chlorophenyl, 2-fluoro-3-chlorophenyl, 4-carbomethoxyphenyl, 4-cyanophenyl, quinolin-2-yl, phenyl, 2-methylthiazol-4-yl, or 4-methoxyphenyl.

20. A compound according to any one of claims 1-19 selected from the group consisting of
N-Benzyloxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 1),
N-(4-Nitro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 2),
N-(2-Nitro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 3),
2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethyl-benzyloxy)-benzamide (compound 4),
2-[(Pyridin-4-ylmethyl)-amino]-N-(2-trifluoromethyl-benzyloxy)-benzamide (compound 5),
N2-[(Pyridin-4-ylmethyl)-amino]-N-(4-trifluoromethyl-benzyloxy)-benzamide (compound 6),
N-(4-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 7),
N-(3-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 8),
2-[(pyridin-4-ylmethyl)-amino]-N-(3,4,5-trimethoxy-benzyloxy)-benzamide (compound 9),
N-(4-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 10),
N-(3-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 11),
N-(2-Chloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 12),
N-(2-Bromo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 13),
N-(2,4-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 14),
N-(3,4-Dichloro-benzyloxy)-2-[(pyridine-4-ylmethyl)-amino]-benzamide (compound 15),

N-(2,6-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 16),
N-(3,5-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 17),
N-(2,3-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 18),
N-(2,5-Dichloro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 19),
N-(2-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 20),
N-(3-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 21),
N-(4-Fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 22),
N-(2-Chloro-6-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 23),
N-(2-Chloro-4-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 24),
N-(3-Chloro-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 25),
4-{2-[(pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid methyl ester (compound 26),
N-(4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 27),
2-[(Pyridin-4-ylmethyl)-amino]-N-(quinolin-2-ylmethoxy)-benzamide (compound 28),
N-Phenoxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 29),
N-(2-Phenoxy-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 30),
N-(3-Phenyl-propoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 31),
N-(2-methyl-thiazol-4 ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide (compound 32),
N-Benzyloxy-2-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide (compound 33),
2-(4-Fluoro-benzylamino)-N-(4-methoxy-benzyloxy)-nicotinamide (compound 34),
2-(4-methoxy-benzylamino)-N-(4-methoxy-benzyloxy)-nicotinamide (compound 35),
N-(1-Phenyl-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-phenoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(Pyridin-2-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(thiazol-4-ylmethoxy)-benzamide,
N-(2-Chloro-thiazol-5-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Phenyl-thiazol-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,

N-(2,6-Dichloro-pyridin-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(2,3,5,6-tetrafluoro-4-methoxy-benzyloxy)-benzamide,
N-(4-Methoxy-3-trifluoromethyl-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(3-trifluoromethoxy-benzyloxy)-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(4-trifluoromethoxy-benzyloxy)-benzamide,
N-(6-Chloro-benzo[1,3]dioxol-5-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Bromo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Iodo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(3-Iodo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
3-{2-[(Pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid methyl ester,
3-{2-[(Pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-benzoic acid,
N-[4-(Morpholine-4-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-{3-[4-(3-Cyano-pyridin-2-yl)-piperazine-1-carbonyl]-benzyloxy}-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[4-(4-Methyl-piperazine-1-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(4-Methyl-piperazine-1-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(Morpholine-4-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(3-Hydroxy-pyrrolidine-1-carbonyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(3-Bromo-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(2-Chloro-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-2-methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-naphthalen-1-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
Acetic acid 2-[3-(2-{2-[(pyridin-4-ylmethyl)-amino]-benzoylaminooxymethyl}-phenyl)-prop-2-ynyloxy]-ethyl ester,
N-[2-(3-Hydroxy-prop-1-ynyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,

N-[3-(3-Hydroxy-prop-1-ynyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[3-(5-Cyano-pent-1-ynyl)-benzyloxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(4-vinyl-benzyloxy)-benzamide,
N-(2-Morpholin-4-yl-2-oxo-ethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-[(2-Methoxy-phenylcarbamoyl)-methoxy]-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
N-Methoxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide,
2-[(Pyridin-4-ylmethyl)-amino]-N-(tetrahydro-pyran-2-yloxy)-benzamide,
N-Benzyloxy-2-[(thiazol-5-ylmethyl)-amino]-benzamide,
N-(2,4-Dichloro-benzyloxy)-2-[(thiazol-5-ylmethyl)-amino]-benzamide,
N-Benzyloxy-2-[(6-chloro-imidazo[2,1-b]thiazol-5-ylmethyl)-amino]-benzamide,
N-Benzyloxy-2-[(2-methyl-imidazo[1,2-a]pyrimidin-3-ylmethyl)-amino]-benzamide,
N-(2,4-Dichloro-benzyloxy)-2-[(2,6-dimethoxy-pyrimidin-4-ylmethyl)-amino]-benzamide,
N-(4-Cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(2-Chloro-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(4-Cyano-2-fluoro-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(3-Bromo-4-cyano-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(2-Iodo-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(4-Cyano-2-methoxy-benzyloxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-(2-Methyl-thiazol-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-nicotinamide,
N-Benzyloxy-2-(isoquinolin-5-ylamino)-nicotinamide,
N-Benzyloxy-2-(4-methoxy-benzylamino)-nicotinamide,
N-Benzyloxy-2-(4-fluoro-benzylamino)-nicotinamide,
N-Benzyloxy-2-(4-chloro-benzylamino)-nicotinamide,
N-(4-Methoxy-benzyloxy)-2-[2-(4-methoxy-phenyl)-vinyl]-nicotinamide,
N-(4-Chloro-benzyloxy)-2-(4-cyano-benzylamino)-benzamide,
2-[4-(Methoxyimino-methyl)-benzylamino]-N-(2-methyl-thiazol-4-ylmethoxy)-benzamide,
N-(4-Cyano-2-methoxy-benzyloxy)-3-[(pyridin-4-ylmethyl)-amino]-isonicotinamide,
N-Benzyloxy-3-[(pyridin-4-ylmethyl)-amino]-isonicotinamide,
N-(2-Methyl-thiazol-4-ylmethoxy)-3-[(pyridin-4-ylmethyl)-amino]-isonicotinamide,
5-Methyl-N-(2-methyl-thiazol-4-ylmethoxy)-2-[(pyridin-4-ylmethyl)-amino]-benzamide, and N-Hydroxy-2-[(pyridin-4-ylmethyl)-amino]-benzamide.

21. A pharmaceutical composition comprising a compound according to any one of claims 1-20 or a pharmaceutically acceptable salt, hydrate, or solvate thereof together with a pharmaceutically acceptable vehicle or excipient.

22. A composition according to claim 21, wherein the amount of active component is in the range of from about 0.1 to about 99.9% by weight of the composition.

23. A composition according to claims 21 or 22 which is in unit dosage form comprising the active component in an amount in the range of from 0.01 to 10000 mg.

24. A composition according to claim 21-23 further comprising another therapeutically active compound selected from the group consisting of chemotherapeutic agents, cytotoxic agents and anticancer agents.

25. A composition according to claim 21-24 further comprising another therapeutically active compound selected from the group consisting of S-triazine derivatives such as altretamine; enzymes such as asparaginase; antibiotic agents such as bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin, epirubicin and plicamycin; alkylating agents such as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine and thiotepa; antimetabolites such as cladribine, cytarabine, floxuridine, fludarabine, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, gemcitabin, pentostatin and thioguanine; antimitotic agents such as etoposide, paclitaxel, teniposide, vinblastine, vinorelbin and vincristine; hormonal agents, e.g. aromatase inhibitors such as aminoglutethimide, corticosteroids, such as dexamethasone and prednisone, and luteinizing hormone releasing hormone (LH-RH); antiestrogens such as tamoxifen, formestan and letrozol; antiandrogens such as flutamide; biological response modifiers, e.g. lymphokines such as aldesleukin and other interleukines; interferon such as interferon-α; growth factors such as erythropoietin, filgrastim and sagramostim; differentiating agents such as vitamin D derivatives and all-trans retinoic acid; immunoregulators such as levamisole; and monoclonal antibodies, tumour necrosis factor α and angiogenesis inhibitors.

26. A compound according to any one of claims 1-20 for use in therapy.

27. A composition according to claim 24 comprising said other therapeutically active compound in a separate container intended for concomitant or sequential administration.

28. A compound according to any one of claims 1-20 for use as antineoplastic agent.

29. The use of a compound according to any one of claims 1-20 for the manufacture of a medicament for the prophylaxis, treatment or amelioration of a disease or condition associated with deregulated angionesis, such as cancer.

30. The use according to claim 29 wherein the medicament further comprises another therapeutically active compound selected from the group consisting of chemotherapeutic agents, cytotoxic agents, and anticancer agents.

31. The use according to claim 30 wherein the other therapeutically active compound is selected from the group consisting of S-triazine derivatives such as altretamine; enzymes such as asparaginase; antibiotic agents such as bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin, epirubicin and plicamycin; alkylating agents such as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine and thiotepa; antimetabolites such as cladribine, cytarabine, floxuridine, fludarabine, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, gemcitabin, pentostatin and thioguanine; antimitotic agents such as etoposide, paclitaxel, teniposide, vinblastine, vinorelbin and vincristine; hormonal agents, e.g. aromatase inhibitors such as aminoglutethimide, corticosteroids, such as dexamethasone and prednisone, and luteinizing hormone releasing hormone (LH-RH); antiestrogens such as tamoxifen, formestan and letrozol; antiandrogens such as flutamide; biological response modifiers, e.g. lymphokines such as aldesleukin and other interleukines; interferon such as interferon-α; growth factors such as erythropoietin, filgrastim and sagramostim; differentiating agents such as vitamin D derivatives and all-trans retinoic acid; immunoregulators such as levamisole; and monoclonal antibodies, tumour necrosis factor α and angiogenesis inhibitors.

32. The use according to claim 30 wherein the other therapeutically active compound is provided in a separate container and intended for concomitant or sequential administration.

33. A method of preventing, treating or ameliorating a disease or condition associated with deregulated angiogenesis, such as cancer, the method comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1-20.

34. A method according to claim 33 further comprising concomitant or sequential administration of one or more other therapeutically active compounds selected from the group consisting of chemotherapeutic agents, cytotoxic agents and anticancer agents.

35. A method according to claim 34 wherein said other therapeutically active compounds are selected from the group consisting of S-triazine derivatives such as altretamine; enzymes such as asparaginase; antibiotic agents such as bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin, epirubicin and plicamycin; alkylating agents such as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine and thiotepa; antimetabolites such as cladribine, cytarabine, floxuridine, fludarabine, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, gemcitabin, pentostatin and thioguanine; antimitotic agents such as etoposide, paclitaxel, teniposide, vinblastine, vinorelbin and vincristine; hormonal agents, e.g. aromatase inhibitors such as aminoglutethimide, corticosteroids, such as dexamethasone and prednisone, and luteinizing hormone releasing hormone (LH-RH); antiestrogens such as tamoxifen, formestan and letrozol; antiandrogens such as flutamide; biological response modifiers, e.g. lymphokines such as aldesleukin and other interleukines; interferon such as interferon-α; growth factors such as erythropoietin, filgrastim and sagramostim; differentiating agents such as vitamin D derivatives and all-trans retinoic acid; immunoregulators such as levamisole; and monoclonal antibodies, tumour necrosis factor α and angiogenesis inhibitors.

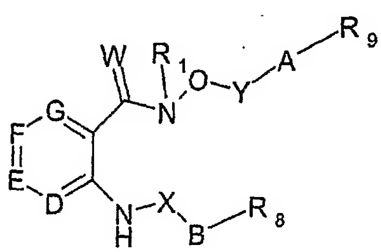
36. A method for treating or ameliorating cancer comprising administering an effective amount of a compound according to any one of claims 1-20 optionally in conjunction with radiation therapy.

37. A method of reducing the metastatic potential of a tumour, the method comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1-20.

38. A method of treating or ameliorating tumours, the method comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1-20.

ABSTRACT

The invention relates to compounds of general formula I



[I]

wherein D, E, F, G, W, Y, R_1, A, R_9, X, B, R_8 are as defined herein, and pharmaceutically acceptable salts, hydrates, or solvates thereof, for use –alone or in combination with one or more other pharmaceutically active compounds- in therapy, for treating diseases associated with deregulated angionesis, such as cancer.

APPENDIX

Figure 1: